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APRIL 1947

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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TREATMENT OF PLASMODIUM VIVAX MALARIA OF FOREIGN ORIGIN

A Comparison of Various Drugs

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IT IS THE purpose of this report to present data concerning the efficacy of various drugs in the treatment of Plasmodium vivax malaria of imported origin. Observations were made on the use of quinacrine hydrochloride (atabrine), quinine sulfate and three drugs known as SN 6911 (3-methyl-4-[4-diethylamino-1-methylbutylamino]-7-chloroquinoline), chloroquine and SN 8137 (4-[3-diethylamino-2-hydroxypropylamino]-7-chloroquinoline).[1] Data on the immediate response to therapy and minor toxic symptoms after the use of all drugs and on the rates of relapse following administration of quinacrine hydrochloride, SN 6911 and chloroquine will be presented in this paper. A separate report will be presented of laboratory studies, including plasma drug concentrations, tests of hepatic function and hematologic and urinary examinations.[2] Some of the data on the patients given quinacrine hydrochloride and quinine sulfate have been included in another report comparing these two commonly used antimalarial drugs.[3]

From the Army Service Forces, Eighth Service Command, Harmon General Hospital, Longview, Texas.

1. The last three drugs were made available by the Board for the Coordination of Malarial Studies through the Office of the Surgeon General of the United States Army, Tropical Disease Treatment Branch. Protocols for the observations were supplied by this board and were followed as closely as local conditions permitted. An article, "Activity of a New Antimalarial Agent, Chloroquine (SN-7618)" (J. A. M. A. **130**:1069 (April 20) 1946) by the Board for the Coordination of Malarial Studies contains a concise summary of the studies under the board, with mention of the principal investigators who worked on fundamental aspects of the drug under the Office of Scientific Research and Development. Presumably, similar articles will be prepared about SN-6911 and SN-8137.

2. Ellerbrook, L. D.; Rhees, M. C., and Lippincott, S. W.: Laboratory Studies of New Drugs in Vivax Malaria of Foreign Origin, to be published.

(Footnotes continued on next page)

SUBJECTS AND METHODS

All the subjects were white soldiers who had contracted malaria in either the Pacific or the Mediterranean area and who had proved relapses while under observation at Harmon General Hospital. In some of the patients, the attacks were "delayed primary" ones, i.e., the first proved attacks of malaria since cessation of the use of suppressive quinacrine hydrochloride. Some of these men had had short bouts of fever overseas, during which either no smear of the blood was made or the result was not known. In 123 patients with malaria acquired in the Pacific area who stated that they had had no proved attacks overseas, a smear positive for organisms was obtained for the first time on an average of forty-six days (standard deviation, thirty-three days) following the stated cessation of the use of quinacrine hydrochloride. The range was from six to two hundred and twenty-five days.[4] In the majority of patients, however, the relapse at this hospital was a recurrence of previously proved malaria. The number of previous attacks, according to the patients' histories, varied from one to nineteen.

No patient was treated unless a smear of his blood was positive for P. vivax and his oral temperature exceeded 100 F. Specific treatment with drugs was always started at 9 a. m. and was given according to the schedules presented here, which, for local convenience, had been modified slightly from the directed protocols. Treatment was postponed on the average for two days after the patient's admission to the treatment ward, because of other studies.[5] Fluids were forced in all patients and sedatives used as necessary. No antipyretics were used. Records were made daily of the incidence of symptoms both before and after beginning of therapy.

The density of parasites was determined in a thin smear taken just before treatment was begun. Smears were then made every twelve hours for five days.

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3. Gordon, H. H.; Christianson, H. B., and Lippincott, S. W.: A Comparison of Quinine and Quinacrine in the Treatment of the Clinical Attacks of Vivax Malaria, South. M. J. **39**:631 (Aug.) 1946.

4. In the studies at Harmon General Hospital which established the Chesson strain of P. vivax (Ehrman, F. G.; Ellis, J. M., and Young, M. D.: Plasmodium Vivax Chesson Strain, Science **101**:377 [April 13] 1945), the intervals from cessation of the use of quinacrine hydrochloride to the appearance of the first smear yielding organisms averaged thirty-two days. These studies were carried out in conjunction with the members of the United States Public Health Service according to a protocol supplied by the Board for Coordination of Malarial Studies. Five patients with neurosyphilis volunteered for the observations. They were given 0.8 Gm. of quinacrine hydrochloride on the first day and then 0.1 Gm. daily for a total of twenty-four days of medication. On the fifth day, when their plasma levels of quinacrine hydrochloride were 16 to 24 micrograms per liter, they were bitten by mosquitoes previously infected from one of our patients who had contracted malaria in New Guinea. Use of quinacrine hydrochloride was then continued for nineteen days, during which time their plasma concentrations varied from 18 to 40 micrograms per liter. Malaria developed in all 5 patients within twenty-five to forty-one days after cessation of use of quinacrine hydrochloride (Malaria Report no. 273 of the Board for Coordination of Malarial Studies from Harmon General Hospital through the Medicine Division, Office of the Surgeon General, Washington, D. C.).

5. Engstrom, W. W.; Gordon, H. H.; Marble, A., and Brunsting, H. A.: Induced Malaria of Foreign Origin, Arch. Int. Med. **79**:185 (Feb.) 1947.

Since it was found that the various drugs in the dosage used produced smears which once sterile remained so, during the latter part of the study the making of smears was discontinued after two sterile ones had been obtained. The single exception was in patients given quinine sulfate; in them, smears were obtained every twelve hours for five or seven days.

On the completion of treatment, the patients were sent to the reconditioning section or other wards of the hospital, whence they reported to the laboratory twice weekly for smears. Smears were examined on the day they were made, and if malarial parasites were found the patient was again transferred to the treatment ward. A follow-up for an arbitrary period of one hundred and twenty days was established in order to determine the rates of relapse. This seemed a reasonable procedure, since previous studies of patients with P. vivax malaria acquired in the Pacific area treated with quinacrine hydrochloride had shown that approximately 90 per cent of the observed relapses took place within one hundred and twenty days after completion of treatment and that extension of the average period of observation to one hundred and forty-three days added few relapses.[6] Although there is evidence to suggest that this may not be true for P. vivax malaria acquired in the Mediterranean area,[7] the data permit comparison of the results following use of the different drugs. The length of the period of observation of nonrelapsers is an important consideration in any discussion of "rates" of relapse.

Some patients were discharged prior to completion of the desired period of observation for administrative reasons; this has been noted in the tables to be presented. Because of the length of the study and occasionally because of the need of other sections in the hospital for beds, patients were given furloughs, usually immediately after completion of treatment. In such instances they were carefully instructed to report to an army hospital for treatment of malarial attacks. In almost all instances, smears positive for organisms were obtained before treatment; a written report of a positive smear was obtained before the relapse was considered a proved one. No attempt was made to determine the rates of relapse following administration of SN 8137 or quinine sulfate.

The dosages of the various drugs and the times of administration are given in table 1. The schedules were set up by the Board for the Coordination of Malarial Studies on the basis of preliminary reports of efficacy and toxicity supplied by both civilian and governmental sources. The protocols permitted the comparison of the effects of (*a*) two different salts, the bisulfate and dinaphthoate, of SN 6911 with quinacrine hydrochloride given in amounts approximating that routinely used in the Army; (*b*) different amounts of chloroquine with each other and with similar dosages of quinacrine hydrochloride over periods of one to six days, and (*c*) all drugs, with quinine sulfate in customary amounts.

All the schedules except one were based on the principle of giving relatively large doses for priming on the first day.[8] With the exception of the patients on

6. Gordon, H. H.; Marble, A.; Lippincott, S. W.; Hesselbrock, W. B., and Ellerbrook, L. D.: Clinical and Laboratory Studies of Relapsing Vivax Malaria of Pacific Origin, New England J. Med. **234**:519 (April 18) 1946.

7. Interim Report on Malaria Relapses After Treatment with Quinine and Synthetic Quinine Substitutes, Malaria Report 377, Board for the Coordination of Malarial Studies, Directorate of Biological Research, Great Britain War Office, London; personal communication to the authors.

8. Shannon, J. A.; Earle, D. P.; Brodie, B. B.; Taggart, J. V., and Berliner, R. W.: The Pharmacological Basis of the Rational Use of Atabrine in the Treatment of Malaria, J. Pharmacol. & Exper. Therap. **81**:307 (Aug.) 1944.

TABLE 1.—*Dosage and Time of Administration of Drugs*

	Quinine	Quinacrine Hydrochloride			SN 6911		Chloroquine				SN 8137
Total Gm.*	16.0 or 30	3.2	2.6	1.2	3.2	3.2	2.0	0.8	1.0	1.2	2.0
Total base, Gm.	13.3 or 25	2.49	2.0	0.94	3.2	3.2	2.0	0.8	1.0	1.2	2.0
Total days	7 or 14	7	6	1	7	7	6	6	1	3	3
Day 1											
9 a.m.	1.0	0.4	0.5	0.5	0.4	0.4	0.4	0.2	0.4	0.4	0.5
5 p.m.	1.0	0.2	0.3	0.3	0.2	0.2	0.2	...	0.2	0.2	0.25
1 a.m.	1.0	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.1	0.25
Day 2											
9 a.m.	1.0	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.25
5 p.m.	1.0	...	...	...	...	...	...	...	...	0.1	...
9 p.m.	1.0	0.2	0.2	...	0.2	0.2	0.2	...	...	...	0.25
Day 3											
9 a.m.	0.64	0.2	0.2	...	0.2	0.2	0.1	0.1	...	0.1	0.25
9 p.m.	0.64‡	0.2	0.1	...	0.2	0.2	0.1	...	...	0.1†	0.25
Day 4											
9 a.m.	0.64	0.2	0.2	...	0.2	0.2	0.1	0.1	...	...	....
9 p.m.	0.64‡	0.2	0.1	...	0.2	0.2	0.1	...	...	...	....
Day 5											
9 a.m.	0.64	0.2	0.2	...	0.2	0.2	0.1	0.1	...	...	....
9 p.m.	0.64‡	0.2	0.1	...	0.2	0.2	0.1	...	...	...	....
Day 6											
9 a.m.	0.64	0.2	0.2	...	0.2	0.2	0.1	0.1	...	...	....
9 p.m.	0.64‡	0.2	0.1	...	0.2	0.2	0.1	...	...	...	....
Day 7											
9 a.m.	0.64	0.2	...	...	0.2	0.2	...	...	...	...	....
9 p.m.	0.64‡	0.2	...	...	0.2	0.2	...	...	...	...	....

* Doses of quinine and quinacrine hydrochloride are in terms of the sulfate and dihydrochloride respectively; others are given in terms of base. SN 6911 was given either as the dinaphthoate or as the bisulfate.

† This dose was given at 5 p. m.

‡ These patients received an additional dose of 0.64 Gm. at 1 p. m. on each day. The patients who received a total of 30 Gm. continued on the schedule for an additional seven days.

TABLE 2.—*Composition of Therapeutic Groups*

Drug	Number of Attacks Treated	Source of Malaria: Pacific "Delayed Primary," %	Source of Malaria: Pacific "Secondary," %	Source of Malaria: Mediterranean, "Secondary," %	Average Number of Previous Attacks: Pacific, Secondary	Average Number of Previous Attacks: Mediterranean Secondary	Distribution of Densities of Parasites per Cu. Mm. Before Treatment: Below 5,000, %	Distribution of Densities of Parasites per Cu. Mm. Before Treatment: Over 5,000, %
Quinine sulfate	55	34	46	20	4	4	70	30
SN 6911								
Disulfate	49	18	64	18	8	8	71	29
Binaphthoate	50	4	82	14	9	6	74	26
Total	99	11	73	16	..	..	73	27
Quinacrine hydrochloride								
3.2	40	10	77	13	7	6	87	13
2.6	51	35	24	41	7	8	65	35
1.2	50	10	78	12	5	7	79	21
Total	141	19	58	23	..	..	78	22
Chloroquine								
2.0	63	30	49	21	4	6	77	23
0.8	55	24	62	14	3	5	81	19
1.0	66	20	58	23	3	8	72	28
1.2	51	37	43	20	3	3	71	29
Total	235	27	53	20	..	..	76	24
SN 8137								
2.0	63	24	75	2	3	7	64	36

this schedule and those given quinine sulfate, all received from 0.6 to 0.8 Gm. of the active base during the first twenty-four hours.

In table 2 data are presented concerning the source of the malaria of the patients in each therapeutic group. It is seen that there was a wide variation in the composition of the groups. This was due to the fact that the various drugs were not tested concurrently and that the composition of the groups of patients who were having malarial relapses fluctuated.

In preliminary analyses of the data no consistent differences were found in the immediate responses to therapy of patients with malaria acquired in the Mediterranean area and those with malaria contracted in the Pacific area. This may be a reflection of the similar distribution of parasitic densities before treatment, a factor which has been shown to affect the rate of disappearance of parasites.[9] Of 122, 318 and 99 patients with "delayed primary" malaria contracted

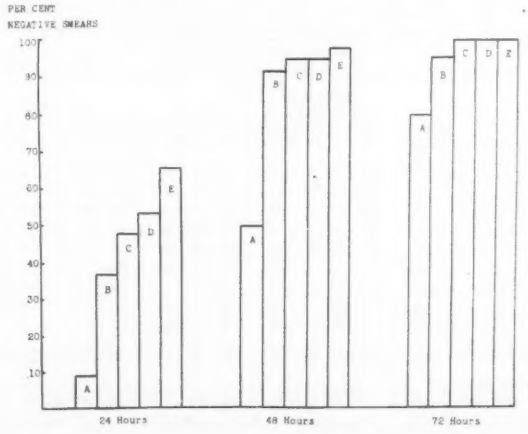

Chart 1.—Rate of disappearance of parasites following treatment with five different drugs. Drug A is quinine sulfate, drug B is SN 6911, drug C is SN 8137, drug D is quinacrine hydrochloride and drug E is chloroquine. The height of each column represents the percentage of smears found to be sterile at the designated time after treatment had been started.

in the Pacific area, secondary malaria contracted in the Pacific area and malaria acquired in the Mediterranean area respectively, 75, 76 and 65 per cent had densities of less than 5,000 per cubic millimeter just before treatment. For all purposes except consideration of rates of relapse, the results have therefore been consolidated to save space in presentation.

RESULTS

Disappearance of Parasites.—Data on the speed of disappearance of parasites are presented in table 3. It is seen that no difference was

9. (*a*) Malaria Report 516, Board for the Coordination of Malarial Studies, from the Harmon General Hospital through the Medicine Division, Office of The Surgeon General, Washington, D. C.; personal communication to the authors. (*b*) Gordon, Christianson and Lippincott.[3]

found between the responses to the two salts of SN 6911. Furthermore, the different doses of chloroquine led to no differences in rates of disappearance of parasites. The results for the five drugs have been summarized in chart 1.

It is seen that at twenty-four hours only 9 per cent of the smears were sterile in the patients given quinine sulfate, as compared with 37 per cent in those given SN 6911 and 48, 53 and 66 per cent in those given SN 8137, quinacrine hydrochloride and chloroquine respectively. By forty-eight hours, use of quinine sulfate had produced only 50 per cent of sterile smears as compared with 92 to 98 per cent for the four other drugs. There can be no question that quinine sulfate is inferior

TABLE 3.—*Rate of Disappearance of Parasites and Percentage of Smears Found Sterile*

Hours After Treatment	Quinine Sulfate	Quinacrine Hydrochloride				SN 6911			Chloroquine					SN 8137
		3.2	2.6	1.2	Total	N	S	Total	2.0	0.8	1.0	1.2	Total	
12	3	18	6	26	17	6	18	12	14	27	27	17	23	8
24	9	55	29	76	53	38	37	37	54	74	68	64	66	48
36	23	88	78	94	87	66	76	71	82	96	91	86	90	84
48	50	99	88	100	95	88	96	92	97	100	97	96	98	95
60	71	99	92	100	97	90	100	95	98	100	100	98	99	100
72	80	100	96	..	99	92	100	96	100	..	100	98	99	100
84	86	100	96	..	99	..	..	..	100	..	..	100	100	...
96	96	..	96	..	99	98	..	99	..	..	..	100	100	...
120	100	..	100	..	100	100	..	100	..	..	..	..	..	...
Number of patients	55	40	51	50	141	50	49	99	63	55	66	51	235	63
Percentage with density over 5,000/c.mm.	30	13	35	21	22	26	29	27	23	19	28	29	24	36

in this regard to the four other drugs tested; whether chloroquine is superior to the other three drugs in clearing the blood of parasites cannot be stated with certainty, because of the fluctuations found in the different subgroups (table 3). These fluctuations may be a reflection of the variations in distribution of densities before treatment (table 2); these in turn may be partial reflections of mechanisms of humoral immunity, which also affect the rate of disappearance of the parasites from the blood.[10] Preliminary analyses have indicated a lack of relationship between plasma levels attained and the rate of disappearance of parasites in these patients, who were given amounts of drugs probably well above the minimum amounts needed to control symptoms. The details will be presented in a separate report.[2]

10. Taliaferro, W. H., and Taliaferro, L. G.: (*a*) Active and Passive Immunity in Chickens Against Plasmodium Lophurae, J. Infect. Dis. **66**:153, 1940; (*b*) The Effect of Immunity on the Asexual Reproduction of Plasmodium Brasilianum, ibid. **75**:1, 1944.

Subsidence of Fever.—Although the synthetic drugs were superior to quinine sulfate in ridding the blood of parasites, all drugs were effective in controlling fever. It is seen that from 71 to 91 per cent of the patients had normal temperatures on the day beginning twenty-four hours after treatment was started. The lowest percentage of normal temperatures on the first day after treatment, 71 per cent, was obtained in the patients given SN 8137. This was associated with the highest incidence of patients who had a rise in temperature on the day treatment was begun, with the fever continuing into the next day. No ready explanation of this is at hand. It may have been due to some specific pyrogenic effect of the drug or to the chance inclusion in this small group of a larger percentage of patients who would have had another paroxysm on the day treatment was begun. Opportunities were not available to study this point.

TABLE 4.—*Time of Subsidence of Fever*

Drug	Number of Patients	Percentage of Patients with Normal Temperature, i. e., Less Than 100 F. on Day Beginning 24, 48 and 72 Hr. After Treatment Was Begun		
		24 Hr.	48 Hr.	72 Hr.
Quinine sulfate	56	78	100	100
Quinacrine hydrochloride	141	91	99	100
SN 6911	99	88	97	99
Chloroquine	236	90	100	100
SN 8137	63	71	100	100

Although no significant differences in the rate of disappearance of parasitemia or fever were found in the subgroups, the clinical impression was obtained that the patients given the smallest dose of quinacrine hydrochloride (1.2 Gm. per day) and chloroquine (0.8 Gm. for six days) continued to feel under par a little longer than those given larger amounts of the drugs. It is also of interest that 1.2 Gm. of quinacrine hydrochloride controlled the fever and parasitemia so well, since the previous disrepute of quinacrine hydrochloride for immediate control of fever and parasitemia was derived from experience with 1.5 Gm. of the drug.[11] The difference is probably accounted for by the fact that in our observations 1.2 Gm. was given in one day, whereas in the discarded schedule only 0.3 Gm. daily for five days was given. The importance of quickly building up plasma concentrations of quinacrine hydrochloride has been demonstrated by Shannon and his co-workers.[8] Evidence will be presented in a separate report that satisfactory concentrations were attained in the present study.[2] No attempts were made to determine the interval until relapse after the one day treatment with

11. Napier, L. E.: The Present Status of Antimalarial Drugs, New England J. Med. **233**:38 (July 12) 1945.

quinacrine hydrochloride. It has already been pointed out that these patients did not feel so well as those given customary doses of quinacrine hydrochloride, and this one day schedule is not suggested as a substitute for the customary schedule of 2.8 Gm. in seven days, which is supported by a wealth of experience.[12]

Minor Toxic Symptoms.—The incidence of minor toxic symptoms is presented in table 5. No symptom was considered attributable to therapy unless it was first noted on the second day of treatment. This criterion seemed desirable in order to avoid confusing minor toxic symptoms resulting from therapy with those of malaria. It is seen that, in general, more minor toxic symptoms followed the administration of

TABLE 5.—*Number of Patients with Minor Toxic Symptoms Attributed to Therapy During Malarial Relapse*

	Drug				
	Quinine Sulfate	Quinacrine Hydrochloride	SN 6911	Chloroquine	SN 8137
Number of patients	55	137	82	236	63
Symptoms *					
Nausea	8	2	5	8	1
Vomiting	0	2	3	2	1
Anorexia	22	2	†	10¶	1
Diarrhea	8	6	6	8	5#
Abdominal cramps	†	†	†	4	1
Dizziness	12	0	0	2	4
Tinnitus	35	0	2	0	2
Diminished hearing	8	0	†	0	0
Blurring of vision	†	†	†	0	2
Pruritus	3	0‡	†	17	4
Urticaria	0	0	0	2	1
Rash	1	†§	0	? 1	1

* No symptom was attributed to therapy unless it was first noted on the day after treatment was begun.

† Records were inadequate for tabulation.

‡ Pruritus was observed in 7 patients not in this series, but all of them had diseases of the skin.

§ Rash occurred in 6 patients not in this series; some of them had active dermatitis.

¶ Both the largest (2.0 Gm.) and the smallest (0.8 Gm.) doses of chloroquine were associated with anorexia in 5 patients each; with the intermediate doses of 1.0 and 1.2 Gm. this was not noted.

Diarrhea, which appeared attributable to the drug, occurred suddenly in 5 patients on the first day of treatment.

quinine sulfate than of the synthetic drugs. Pruritus developed in 17 patients, or 7 per cent, of those given chloroquine which was not associated with rash but which produced considerable discomfort in some patients. This was seen six times in patients given 2.0 Gm. and six times in patients given only 1.2 Gm. of the drug.

12. (*a*) Dieuaide, F. R.: Clinical Malaria in Wartime, War Med. **7**:7 (Jan.) 1945. (*b*) Hudson, E. H.: Quinine and Atabrine: Development and Present Application, U. S. Nav. M. Bull. **45**:57 (July) 1945.

The newer synthetic drugs had no particular advantages over quinacrine hydrochloride with respect to toxic symptoms except that they could be given to patients who were sensitive to quinacrine hydrochloride. These were essentially of two groups. The first consisted of a number of patients from the section of dermatology who had eczematoid dermatitis or atypical lichen planus, in the causation of which quinacrine hydrochloride may have played a part.[13] Attempts to treat their malaria with quinacrine hydrochloride led to pronounced exacerbation. Treatment of some of these with chloroquine or SN 8137 controlled the malaria without deleterious effect on the disease of the skin. The second and much smaller group consisted of the rare persons in whom severe vomiting and diarrhea developed even with administration of small doses of quinacrine hydrochloride. In both of these groups in the past, quinine sulfate, which is inferior to quinacrine hydrochloride not only because of its greater incidence of production of minor toxic symptoms but because of the shorter interval until relapse,[14] would have had to be given. The case of a patient sensitive to quinacrine hydrochloride for whom one of the new synthetic drugs was a boon is illustrated in the following report of a chronic carrier of Plasmodium falciparum who was apparently successfully treated by the administration of SN 6911.

The patient, a 35 year old white soldier, was admitted to Harmon General Hospital on June 22, 1944, with a transfer diagnosis of chronic malaria due to P. falciparum. According to his past history, he had contracted malaria of unknown type while in Spain in 1936. He stated that he had had two mild recurrences in Spain in 1937 and one in California in 1939. He was inducted into the United States Army on May 15, 1942 and served in North Africa, Sicily and Italy from June 1943 until his return to the United States in January 1944. He had been in Army hospitals because of malaria on six occasions before the hospitalization, in November 1943, which led to his evacuation to the United States. Records from the hospitals accompanying the patient indicated that smears were positive for malarial parasites in November 1943, January, February, March, April, May and June 1944. During each of these months except January, when the type of parasite was not reported, the smears were repeatedly positive for P. falciparum. During this period of eight months the patient was treated with quinine sulfate, oxophenarsine hydrochloride, and quinacrine hydrochloride, although there was one note indicating that he was "unable to take quinacrine hydrochloride."

On June 29, seven days after his admission to this hospital, a smear was obtained because he complained of weakness. Although he had no fever, the smear contained gametocytes of P. falciparum. He was transferred to the treatment ward, where his temperature rose to 100.4 F., and he complained of generalized aches. On June 30, a smear was again positive for malarial parasites, this time for both P. falciparum and P. vivax. A smear taken on the morning of July 1 contained only P. vivax. At this time, he was persuaded to take quinacrine

13. Livingood, C. S., and Dieuaide, F. R.: Untoward Reactions Attributable to Atabrine, J. A. M. A. **129**:1091 (Dec. 15) 1945.

14. (*a*) Green, R. A.: Totaquine in the Treatment of Malaria, Bull. U. S. Army M. Dept., January 1945, no. 84, p. 51. (*b*) Dieuaide.[12a]

hydrochloride, although he stated that he had never been able to retain it. He was given 0.4 Gm. at 9 a. m., and at 2 p. m. he vomited brightly yellow-stained material. Administration of quinacrine hydrochloride was discontinued, and on July 2 he was started on SN 6911 dinaphthoate. The smear taken just prior to treatment was sterile, but he had a slight chill, with a rise in temperature to 101.8 F., during the early afternoon. Smears taken daily during seven days of treatment and twice weekly thereafter were sterile for the next month. On August 7 he was admitted to the treatment ward again because of a slight chill and a temperature of 100 F. His smear was positive for P. vivax. His temperature rose to 101.4 F. on the afternoon of August 7, was normal on August 8 and rose to 104.2 F. at noon of August 9. Use of SN 6911 dinaphthoate was started on the morning of August 9, with good clinical response. Smears were positive daily for P. vivax from August 7 to August 12 inclusive but remained sterile on daily examination until

TABLE 6.—*Rates of Relapse Following Treatment of "Delayed Primary" Attacks of Malaria Acquired in the Pacific Area*

		Relapsers					Nonrelapsers			
				Time Until Relapse, Days				Period of Observation, Days		
Drug	Total Number of Patients	Total Relapses	Sixty Day "Relapse Rate," %	Mean	Minimum	Maximum	Number	Mean	Minimum	Maximum
Quinacrine hydrochloride										
3.2/7 days or 2.6/6 days	22	17	77	66	30	192	5	121	86	189
SN 6911 N and S										
3.2/7 days	13	12	92	46	29	76	1	112	..	..
Chloroquine										
2.0/6 days	19	12	63	54	36	75	7	98	75	122
1.2/3 days	14	11	79	63	41	121	3	93	81	108
1.0/1 day	11	10	91	54	39	89	1	176	..	..
0.8/6 days	13	9	69	75	27	131	4	121	97	161
Total	57	42	74	61	27	131	15	108	75	176

August 16 and on twice weekly examinations until discharge on October 26. During this period he was admitted to the wards of the hospital from the reconditioning section on two occasions, once because of acute tonsillitis and once because of acute alcoholism; neither of these illnesses precipitated malaria.

In summary, this patient, who tolerated quinacrine hydrochloride poorly, had blood smears repeatedly positive for P. falciparum over a period of eight months. The administration of SN 6911 dinaphthoate brought his symptoms under control, and repeated smears taken over a period of four months remained negative for P. falciparum. Apparently, this drug cured this soldier of P. falciparum infection just as quinacrine hydrochloride would have done [12a] and was effective where quinacrine hydrochloride had failed because of his intolerance.

Rates of Relapse.—Rates of relapse following treatment with quinacrine hydrochloride, SN 6911 and chloroquine are presented in tables 6, 7 and 8 for patients with "delayed primary" and secondary attacks of malaria acquired in the Pacific and Mediterranean area respectively. The term "sixty day rate of relapse" has been used to indicate that no patient was considered a nonrelapser unless he had been observed for

at least sixty days following completion of treatment. As previously stated, it had been originally planned to observe all nonrelapsers for at least one hundred and twenty days. Administrative reasons, however, made this impossible in some cases. For each group of patients, there-

TABLE 7.—*Rates of Relapse Following Treatment of "Secondary" Attacks of Malaria Acquired in the Pacific Area*

		Relapsers					Nonrelapsers			
				Interval to Relapse, Days				Period of Observation, Days		
Drug	Total Number of Patients	Total Relapses	Sixty Day "Relapse Rate," %	Mean	Minimum	Maximum	Number	Mean	Minimum	Maximum
Quinacrine hydrochloride										
3.2/7 days or 2.6/6 days	39	26	67	63	34	120	13	100	78	129
SN 6911 N and S										
3.2/7 days	62	37	70	48	18	89	25	87	62	147
Chloroquine										
2.0/6 days	30	18	60	56	43	81	12	103	62	127
1.2/3 days	13	9	69	58	41	91	4	110	62	132
1.0/1 day	35	29	83	56	39	154	6	127	106	158
0.8/6 days	33	27	82	57	36	113	6	122	76	153
Total	111	83	75	57	36	154	28	113	62	158

TABLE 8.—*Rates of Relapse Following Treatment of "Secondary" Attacks of Malaria Acquired in the Mediterranean Area*

		Relapsers					Nonrelapsers			
				Interval to Relapse, Days				Period of Observation, Days		
Drug	Total Number of Patients	Total Relapses	Sixty Day "Relapse Rate," %	Mean	Minimum	Maximum	Number	Mean	Minimum	Maximum
Quinacrine hydrochloride										
3.2/7 days or 2.6/6 days	26	15	58	69	32	108	11	128	96	141
SN 6011 N and S										
3.2/7 days	15	14	93	56	29	101	1	183	..	..
Chloroquine										
2.0/6 days	12	2	17	57	43	70	10	111	69	166
1.2/3 days	8	5	63	54	45	72	3	101	82	132
1.0/1 day	14	6	43	57	38	75	8	134	119	164
0.8/6 days	6	4	67	54	38	74	2	138	127	148
Total	40	17	43	55	38	75	23	120	69	166

fore, the average period of observation of nonrelapsers has been indicated. Lengthening of this period would tend to increase the rate of relapse and also to increase the mean interval until relapse occurred.

With these qualifications in mind, it is seen in tables 6 and 7 that high rates of relapse, from 63 to 93 per cent and from 60 to 83 per cent, were found following treatment of "primary" and secondary attacks respectively of malaria acquired in the Pacific area. None of the drugs

had any superiority over the others, and the administration of different doses of chloroquine resulted in no striking differences.

It is further seen that there were no differences between the rates following "primary" and secondary attacks. Since the groups are small, however, it would not be justifiable to assume that the same results would be obtained in large organizations.

In malaria acquired in the Mediterranean area widely fluctuating results were obtained. Following the use of chloroquine the rates of relapse averaged 43 per cent, varying from 17 to 63 per cent. Following the use of quinacrine hydrochloride and SN 6911 the rates were 58 and 93 per cent. The cause for this variability is not obvious, but it may be explained by the smallness of the groups and possibly by the greater variation in the number of strains and amount of infection which the patients contracted in North Africa, Sicily and/or Italy. In a study of mosquito-induced malaria, a much lower rate of relapse was observed following delayed treatment with quinacrine hydrochloride of malaria contracted in the Mediterranean area than following the same treatment of malaria contracted in the Pacific area, suggesting an essential difference between the malaria from these two sources.[15] Further evidence for such a difference is the longer interval until a delayed primary attack of malaria contracted in the Mediterranean area (one hundred and fifty-four to one hundred and eighty-two days in 3 patients observed in this hospital and two hundred days in the patient of Cavanaugh[16]), as compared with the average of forty-six days in our patients with delayed primary attacks of malaria acquired in the Pacific area.

Intervals Until Relapse Following Treatment.—The intervals until relapse following treatment are given in table 9 for the patients with malaria acquired in the Pacific area. No data are presented on the intervals until relapse of malaria contracted in the Mediterranean area, because of the small number in each therapeutic group. It is seen that the majority of relapses took place from the fifth to the ninth week following cessation of treatment with any of these drugs. The various doses of chloroquine led to no significant differences in the time at which relapses occurred. Following the use of SN 6911, thirteen, or 27 per cent, of the observed relapses occurred during the first five weeks after treatment, as compared with only 7 per cent following the administration of quinacrine hydrochloride and 2 per cent following use of chloroquine.

15. Gordon, H. H.; Marble, A.; Engstrom, W. W.; Brunsting, H. A., and Lippincott, S. W.: Relapses Following Delayed Treatment of Naturally Induced Vivax Malaria of Pacific Origin, Science **103**:391 (March 29) 1946.

16. Cavanaugh, R. L.: Malaria Appearing After Discontinuance of Atabrine Prophylaxis, Bull. U. S. Army M. Dept., December 1944, no. 83, p. 120.

In this respect, chloroquine is apparently superior to SN 6911 as a substitute for quinacrine hydrochloride.

No attempt was made to determine the rates of relapse following the use of quinine sulfate or SN 8137. Fifteen patients treated in this hospital with quinine sulfate had proved relapses while under observation; ten of these occurred between nine and twenty days after completion of treatment. In the whole group of 217 patients with relapses following treatment with the synthetic drugs, only 1 patient had a relapse within the first three weeks. Six relapses have been seen following the use of SN 8137; these occurred within thirty-one to

TABLE 9.—*Interval Until Relapse in Malaria Acquired in the Pacific Area*

Days to Relapse	Quinacrine Hydrochloride		SN 6911		Chloroquine									
					Total		2.0		1.2		1.0		0.8	
	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %
1-7	0	..	0	..	0	..	0	..	0	..	0	..	0	..
8-14	0	..	0	..	0	..	0	..	0	..	0	..	0	..
15-21	0	..	1	2	0	..	0	..	0	..	0	..	0	..
22-28	0	..	2	6	1	1	0	..	0	..	0	..	1	3
29-35	3	7	10	27	1	2	0	..	0	..	0	..	1	6
36-42	3	14	5	37	18	16	4	13	2	10	6	15	6	22
43-49	9	35	8	53	36	45	6	33	7	45	16	56	7	42
50-56	8	53	13	80	18	59	6	53	3	60	2	62	7	61
57-63	4	63	3	86	23	78	9	83	2	70	9	85	3	69
64-70	2	67	2	90	5	82	1	87	1	75	2	90	1	72
71-77	3	74	2	94	9	89	3	97	2	85	1	92	3	81
78-84	4	84	1	96	2	90	1	100	0	85	1	95	0	..
85-90	1	86	2	100	3	93	..	..	0	85	1	97	2	86
91-120	5	98	..	..	5	97	..	..	2	95	0	..	3	94
121-150	0	..	..	..	3	99	..	..	1	100	0	..	2	100
151-180	0	..	..	..	1	100	..	..	..	..	1	100	..	..
181-210	1	100	..	..	..	..	..	..	..	..	..	..	..	..
Total	43		49		125		30		20		39		36	

thirty-nine days following completion of treatment, indicating that relatively early relapses can occur with administration of this drug as well as of the other synthetic drugs.

COMMENT

As part of the drug-testing program of the Board for Coordination of Malarial Studies, three synthetic drugs, SN 6911, chloroquine and SN 8137, were made available for comparison with quinacrine hydrochloride in the treatment of soldiers with relapsing P. vivax malaria of foreign origin. The achievement of two main purposes was desired. The first and most important was to find a drug which would be truly curative and therefore preferable to quinacrine hydrochloride. The second was to find a drug as efficacious as quinacrine hydrochloride in

the acute attack but without minor disadvantages such as staining of the skin or major disadvantages such as unsuitability in patients with natural or acquired sensitivity to the drug.

Although significant gastrointestinal intolerance occurs only rarely, the extensive use of quinacrine hydrochloride as a suppressive agent has been associated with the development of dermatitis in a considerable number of soldiers. The actual incidence of this condition is low, but the treatment of malaria or the continued need for suppressive treatment in these soldiers is a problem because of the inferiority of quinine sulfate to quinacrine hydrochloride. All three new synthetic drugs tested proved to be satisfactory substitutes for quinacrine hydrochloride in their ability to control the acute attacks of malaria and in the low incidence of production of minor toxic symptoms when used in the doses described. Furthermore, they were well tolerated by patients who were intolerant to quinacrine hydrochloride. Several patients whose dermatitis showed exacerbation under treatment in this hospital with quinacrine hydrochloride took the prescribed doses of chloroquine and SN 8137 without difficulty. None of these men were given suppressive therapy over long periods with the new synthetic drugs to test the possible development of sensitivity to them. One patient who was a chronic carrier of P. falciparum for eight months was apparently cured during a four month observation period by the administration of SN 6911, just as he would have been cured had he been able to ingest and retain quinacrine hydrochloride.

The most important goal, however, complete cure, was not attained. The rates of relapse remained high in malaria contracted in the Pacific and Mediterranean areas and were not significantly different from those observed following routine treatment with quinacrine hydrochloride. As indicated, some differences were found in the intervals until relapse, relapses coming at a shorter interval following use of SN 6911 than following use of quinacrine hydrochloride or chloroquine. Presumably this is due to differences in the rate of disappearance of these antimalarial drugs from fluids in the body.

Another factor which might affect the occurrence of a relapse and the interval is the person's "immunity." This is a complex subject,[17] but, theoretically, decreases in either intracellular or extracellular factors or both might be responsible for the reappearance of parasites in the peripheral blood. Because the density of parasites just before treatment might be considered an index of immunity, an attempt was made to relate this to incidence of relapses. No such relationship was found. An attempt was then made to relate it to the interval until relapse; these

17. (*a*) Coggeshall, L. T.: Immunity in Malaria, Medicine **22**:87 (May) 1943. (*b*) Taliaferro, W. H.: Immunity in Malaria, Am. J. Clin. Path. **14**:593 (Dec.) 1944.

data are presented in chart 2 for three groups of patients treated with SN 6911 (3.2 Gm.), quinacrine hydrochloride (2.6 or 3.2 Gm.) and chloroquine (1.0 or 1.2 Gm.). It is seen that within each therapeutic

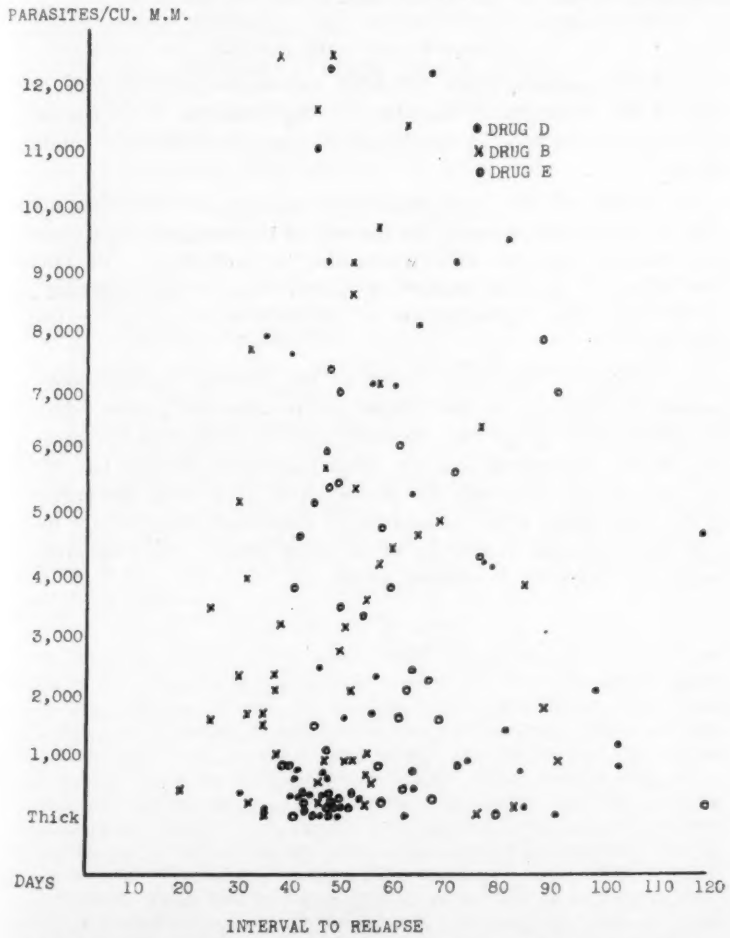

Chart 2.—Relationship of density of parasites to the time of relapse in P. vivax malaria contracted in the Pacific area. Drug B is SN 6911 (3.2 Gm. of base in seven days); drug D is quinacrine hydrochloride (3.2 or 2.6 Gm. in seven or six days), and drug E is chloroquine (1.0 or 1.2 Gm. of base in one or three days). Interval until relapse is given in days following completion of treatment.

group there was no relationship between the interval until relapse following treatment and the density of parasites just before treatment. Patients who had so few parasites that they were found in only a thick

smear relapsed in as early as forty and as late as one hundred and twenty days; patients who relapsed at fifty days had densities varying from smears which were positive for organisms only when thick to smears containing as high as 12,000 per cubic millimeter and over.

SUMMARY AND CONCLUSIONS

1. Three synthetic drugs, SN 6911, chloroquine and SN 8137, were used in the treatment of relapsing P. vivax malaria of foreign origin in doses recommended by the Board for the Coordination of Malarial Studies.

2. Neither SN 6911 nor chloroquine was more effective than quinacrine hydrochloride in curing the patients of relapses, and some evidence was collected that SN 8137 would also be ineffective. The interval until relapse in a small number of patients was shorter following use of SN 6911 than following use of chloroquine or quinacrine hydrochloride.

3. All three drugs were found to be effective in controlling the parasitemia and fever of the relapse and to cause the patient relatively few minor toxic symptoms. Because none of them stain the skin and because the widespread use of quinacrine hydrochloride has led to the development of sensitivity to the drug in a small percentage of soldiers, the drugs tested may prove of value as a substitute for quinacrine hydrochloride in therapy of the acute attack. All four synthetic drugs were superior to quinine sulfate.

COEXISTING TUBERCULOSIS AND COCCIDIOIDOMYCOSIS

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THE COEXISTENCE of active tuberculosis and coccidioidomycosis is rare. Smith [1] has reported the cases of many persons who have had positive reactions to tuberculin tests of the skin with active coccidioidal infections. He further described the similarity of physical and roentgenologic findings in the two diseases. Cherry and Bartlett [2] have recently reported a case of coexisting active tuberculosis and coccidioidal infection. Smith [3] mentioned the presence of coccidioidal infection superimposed on active tuberculosis. He described 1 patient with a tuberculous effusion on one side in whom a coccidioidal effusion developed on the other side. We present a case of a spontaneous hydropneumothorax in which were isolated both Coccidioides immitis and Mycobacterium tuberculosis.

REPORT OF A CASE

The patient is a 27 year old white soldier who entered the hospital complaining of shortness of breath on exertion. His past history revealed no significant medical or surgical diseases. In September 1943, while on duty in the desert training area of California, he first became aware of weakness, fatigue and pain in the left pleural area. He was hospitalized in a field hospital and after a short period of observation was transferred to a station hospital, where a diagnosis of coccidioidomycosis was made by roentgenologic examination and the finding of double-contoured spherules of C. immitis in the sputum. He was given complete rest in bed, and after five months he was discharged to full military duty as apparently cured. Further details of this hospitalization are not available. During the period from March 1944 to August 1944 the patient was on active duty, complaining of intermittent pain in the pleural area bilaterally which was mild and

From the Laboratory Service, Regional Hospital, Fort Jay, N. Y., and the laboratory, medical and roentgenologic services, Rhoads General Hospital, Utica, N. Y.

1. Smith, C. E.: Parallelism of Coccidioidal and Tuberculous Infections, Radiology **38**:643-648 (June) 1942.

2. Cherry, C. B., and Bartlett, A. G.: The Diagnosis of Acute Coccidioides Immitis Infections, Bull. U. S. Army M. Dept. **5**:190-193 (Feb.) 1946.

3. Smith, C. E.: Personal communication to the authors.

nonincapacitating. Repeated physical and roentgenologic examinations of his chest during this period revealed no abnormalities. In August 1945, while in the European Theater of Operations, he began to complain of sore throat and blood-streaked sputum. This was followed by weakness, pain in the right side of the chest and malaise. The pain in the chest was sharp in intensity and was increased by deep breathing, coughing or sudden movements. He was admitted to an overseas general hospital on Aug. 6, 1945. During this hospitalization the temperature ranged between 98.6 and 100.4 F., the pulse rate ranged from 90 to 110 and the blood pressure was 130 systolic and 84 diastolic. Roentgenologic examination revealed pronounced collapse of the right lung, with a hydropneumothorax involving the right side. The patient was given complete rest in bed. Repeated thoracenteses were performed, from 1,500 to 2,000 cc. of fluid being removed during each procedure. No expansion of the collapsed lung was noted. The fluid was straw colored, with a specific gravity range between 1.018 and 1.022. Bacteriologic examination revealed a sterile fluid. Cytologic examination revealed from 2,000 to 2,500 white blood cells, with a differential count of 75 per cent polymorphonuclear leukocytes and 25 per cent lymphocytes. Yeasts, fungi or molds were not noted on direct smear. Acid-fast stains yielded normal results. The peripheral white blood cell count varied between 10,000 to 10,500, with 60 to 65 per cent neutrophils and 35 to 40 per cent lymphocytes. The erythrocyte sedimentation rate (Westergren) varied between 15 and 18 mm. per hour. Smears were negative for malarial parasites. The patient was subsequently evacuated to the Zone of the Interior as a litter patient, with a diagnosis of hydropneumothorax involving the right side, cause unknown.

On Nov. 10, 1945 he was admitted to the Rhoads General Hospital, complaining of weakness and dyspnea on slight exertion. Physical examination revealed a well nourished white man in no apparent distress. There was no evidence of cyanosis, jaundice or edema. There was a slight shift of the trachea to the left. The thorax appeared symmetric in outline. The right hemithorax did not move with respiration. Percussion revealed dulness over the upper two thirds of the right lung, changing to flatness in the region of the lower third. Breath sounds were absent except over the paravertebral area of the right lung, where distant bronchial breath sounds were noted. Vocal egophany was notably present on the right side. The coin test gave a positive result over the upper third of the right side of the chest. Metallic tinkles were heard following inspiration, which suggested the passage of air through the fluid. The left lung was clear. Palpation revealed a slight shift of the heart to the left, but otherwise no remarkable features were noted. The remainder of the physical examination revealed no abnormalities.

Course in the Hospital.—The patient was afebrile throughout this period of hospitalization. He gained weight and noted the progressive disappearance of the exertional dyspnea. Roentgenologic studies, which are reported in detail here, revealed the presence of a collapsed right lung, with a large hydropneumothorax. Aspiration of the right side of the chest was performed on three different occasions. During the first two aspirations 1,500 cc. of cloudy yellow-brown fluid was removed. The last thoracentesis, performed six weeks later, was productive of 300 cc. of clear amber fluid. Detailed laboratory studies of the fluid are reported in succeeding paragraphs. No air was replaced after the removal of large amounts of fluid, and the lung revealed no reexpansion. This, together with the physical findings, suggested the presence of a patent bronchopleural fistula. It was felt that it was probably high in the apex, since the patient did not cough or expectorate to any degree.

Bronchoscopy was performed and revealed a normal tracheobronchial tree except for some shortening on the right side, which was to be expected in view of the collapsed right lung. Solution of methylene blue was instilled into all divisions of the right bronchus but could not be subsequently recovered in the pleural fluid.

Reaction to a coccidioidin test of the skin, in a dilution of 1 : 100, was negative on November 22 but was definitely positive when the test was repeated six weeks later. The reaction to a tuberculin test of the skin was positive in a dilution of 1 : 1,000,000.

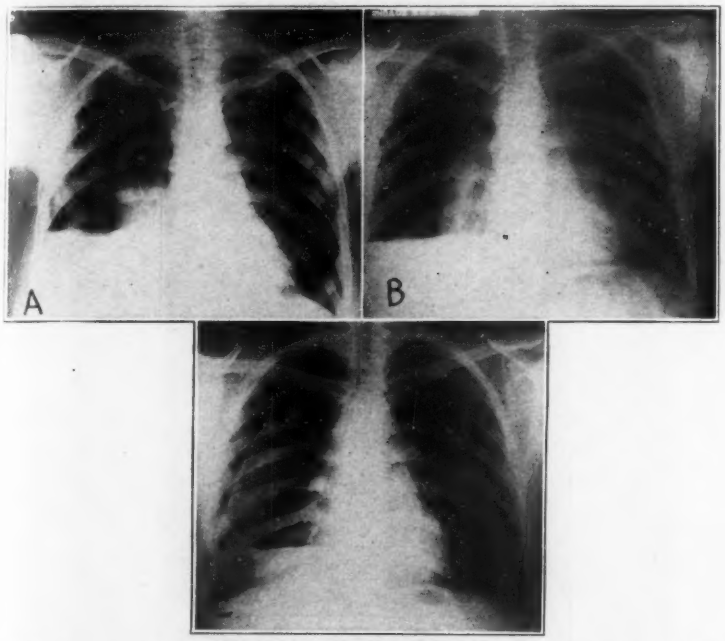

Fig. 1.—*A*, roentgenogram of the chest four weeks following the onset of the present illness. Note the extensive hydropneumothorax involving the right side and the symmetric collapse of the right lung; the arrow points to a discrete leison in the left parahilar region. *B*, roentgenogram in the fourteenth week of illness. Note the disappearance of adhesions, with almost complete collapse of the right lung. *C*, roentgenogram in the twenty-third week of illness. Note the definite reexpansion of the right lung.

The patient continued to improve during this hospitalization, but, in view of the persistent collapse of the right lung and the reasonable assumption of the existence of an open bronchopleural fistula, surgical correction was considered. However, serial roentgenologic studies revealed beginning expansion of the right lung on Dec. 29, 1945, which has since continued progressively. It is presumed that spontaneous closure of the fistula has occurred. Conservative treatment has since been continued. The patient is asymptomatic, with no evidence of disseminated lesions.

Roentgenologic Studies.—At the time of the first roentgenogram, four weeks following the onset of the present illness (fig. 1 *A*), a massive pleural effusion on the right side had been partially replaced by a pneumothorax. The right lung was collapsed symmetrically, and numerous thick adhesions crossed between the lung and the wall of the chest. A few pockets of fluid remained. For several weeks the fluid reaccumulated. Repeated drainage was performed, and no air was injected into the pleural cavity. A roentgenogram (fig. 1 *B*) in the fourteenth week of illness showed a complete collapse of the right lung, with massive pneumothorax. All adhesions had disappeared, and the collapsed lung was covered

Fig. 2.—Sabouraud's maltose peptone agar medium. Note the snow white, fluffy and flakelike growth of C. immitis isolated from the pleural fluid.

by a layer of thickened pleura, varying from 5 to 20 mm. in thickness. The remaining pleural fluid was still freely movable. The right lung remained collapsed for several weeks and then slowly and evenly began to reexpand. Figure 1 *C*, taken at the twenty-third week, shows a 60 per cent reexpansion of the lung. The thickened visceral pleura had disappeared. Neither hilus was enlarged. No parenchymal infiltration was visible in the right lung.

A discrete, stationary lesion in the opposite lung (fig. 1 *A*, arrows) had been observed during the entire period of the present illness. It was firm, round and sharply defined and was in the left parenchyma close to the hilus. No cavity or calcium was observed in it. The adjacent hilus was not enlarged.

Laboratory Data.—On admission the red and white blood cell counts were 4,420,000 and 9,650 respectively, and the hemoglobin content was 94 per cent. A differential white blood cell count revealed 62 per cent neutrophils, 34 per cent lymphocytes and 4 per cent monocytes. The erythrocyte sedimentation rate (Westergren) on admission revealed an elevation to 16 mm. per hour. The initial and subsequent urinalyses revealed no abnormalities. Smears of the blood

Fig. 3.—Direct smear from a culture of C. immitis. Note the mycelial network with branching hyphae and conidia. × 980.

were persistently negative for malarial parasites. Repeated blood cell counts revealed a white blood cell count ranging between 8,500 and 9,750, with a differential range of 60 to 65 per cent neutrophils, 30 to 35 per cent lymphocytes and 2 to 3 per cent monocytes. Daily sedimentation rates varied between 14 and 18 mm. per hour. Examination of the sputum showed occasional nonhemolytic streptococci. Extensive search failed to reveal yeasts, fungi or molds. Studies for the presence of acid-fast bacilli disclosed none. Repeated examinations of

gastric contents did not reveal tubercle bacilli. Ziehl-Neelsen staining of direct smears from the pleural fluid revealed Myco. tuberculosis. No myceliums were noted. The fluid was cultured on Sabouraud's maltose peptone agar and on Petragnini's medium. In four days small elevated waxy-like oval and round plaques measuring 3 to 10 mm. in diameter were observed on Sabouraud's medium. Within fourteen days these plaques were covered and surrounded by a snow white, fluffy and flakelike growth which penetrated deep into the medium (fig. 2). Smears from this culture revealed an intricate mycelial network with long branching septate hyphae with a formation of conidia and chlamydospores (fig. 3). Cultures were sent to the Registry of Fungous Diseases, Duke University School

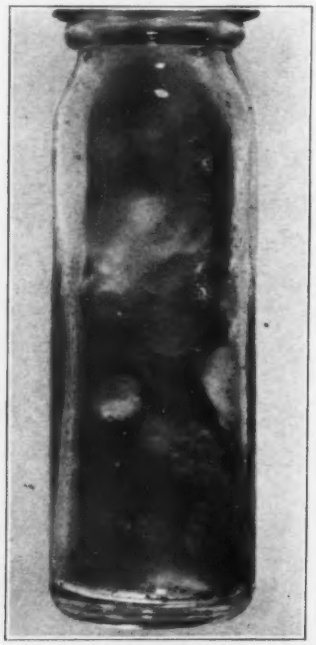

Fig. 4.—Culture on Petragnini's medium. Note the fluffy white growth of C. immitis surrounding the confluent coarse gray-brown dirty growth of Myco. tuberculosis.

of Medicine, from which a confirmatory diagnosis of C. immitis was received. On the Petragnini medium a similar growth of C. immitis was noted on the seventh day, which reached maximum growth on the twenty-fifth day. On the fourth week numerous hard, wrinkled, elevated, coarse, brown-yellow colonies, measuring 14 to 18 mm. in diameter, were noted on this culture medium. Smears revealed characteristic tubercle bacilli. On the fifth week it was of great interest to note the Petragnini medium, on which was growing a coarse, homogeneous, confluent, dirty gray-brown growth of Myco. tuberculosis, surrounded by a fluffy, snowlike growth of C. immitis, the two apparently growing independently of each other (fig. 4).

Pleural fluid (5 cc.) was injected subcutaneously into the right groin of an adult male guinea pig. Seventeen days later the pig exhibited a swollen right testicle. The overlying skin was reddened and edematous. Microscopic examination of the testis revealed a suppurative orchitis. The draining lymph nodes were enlarged two to four times their usual size and were soft. On section, the entire nodal parenchyma was converted into a soft, yellow-gray necrosuppurating mass. Histologic examination revealed complete loss of nodal architecture. The lymphoid follicles could not be made out but were replaced by small granulomatous foci consisting of pyknotic lymphocytes, polymorphonuclear leukocytes and large mononuclear histiocytes. A number of these foci exhibited central necrotic cores consisting predominantly of karyorrhectic and karyolytic polymorphonuclear leukocytes. Within and occupying the central portions of the granulomas were double-contoured spheres measuring 10 to 50 microns in diameter (figs. 5 and 6). Within these spherules were numerous endospores. Budding was not observed. Interspersed throughout the cellular elements were large multinucleated giant cells

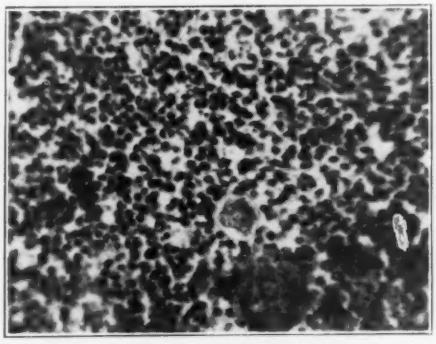

Fig. 5.—Focal granuloma from the inguinal lymph node of a male guinea pig. Note the double-contoured spherule of C. immitis. × 450.

of the Langhans type. The nuclei were deeply pyknotic and aggregated peripherally. The cytoplasm of these giant cells contained numerous spherules. However, a number of these granulomas revealed central eosin-staining caseation, surrounded by palisades of epithelioid cells containing clear reticular cytoplasm with deep vesicular nuclei. Scattered throughout were other Langhans' giant cells, the cytoplasm of which did not contain the characteristic spherules (fig. 7). Acid-fast stains revealed tubercle bacilli in these foci. Cultures of material from the lymph nodes on Sabouraud's and Petragnini's medium revealed beginning growth of C. immitis and Myco. tuberculosis within four and twenty-six days respectively. Serum was sent to the Stanford University School of Medicine, Department of Public Health and Preventive Medicine, for confirmatory serologic tests for coccidioidal infection. A complement fixation test gave a positive reaction (4 plus and 2 plus) in dilutions of 1 : 2 and 1 : 4 respectively but elicited a negative reaction in higher dilutions. A precipitin test with undiluted antigen gave a negative reaction. The conclusion reached from these serologic examinations were that the "findings indicate a coccidioidal infection which occurred a considerable time in the past and which does not seem to be progressive."

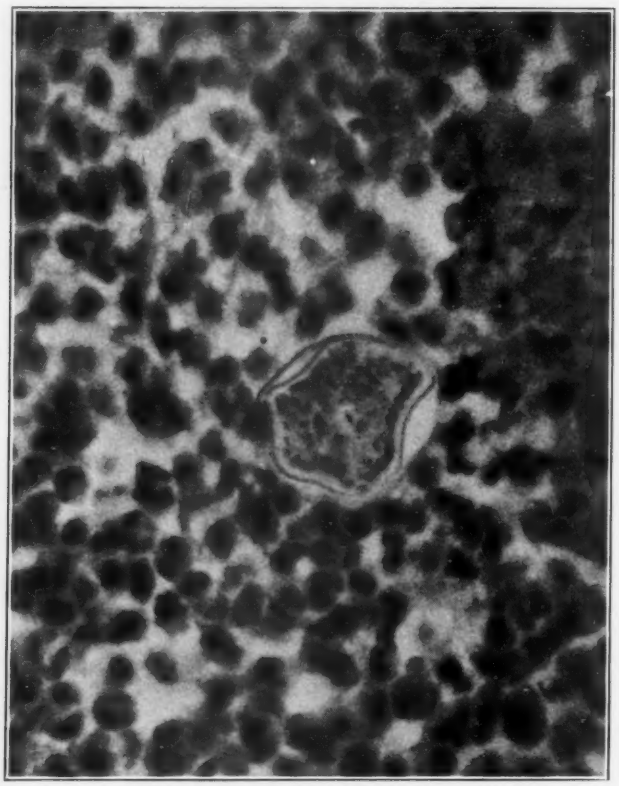

Fig. 6.—C. immitis. The immediate type cell surrounding the organism is a polymorphonuclear leukocyte. × 980.

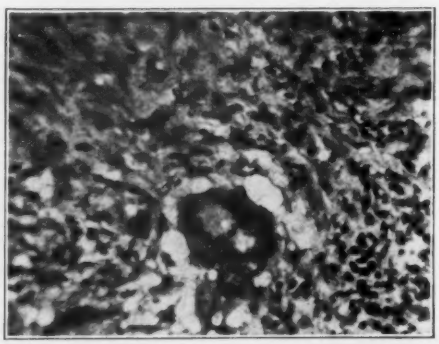

Fig. 7.—Multinucleated giant cell in a tuberculous focus. Note the concentric palisading of epithelioid cells. C. immitis is not present here. Ziehl-Neelsen stains reveal tubercle bacilli in this area. × 450.

COMMENT

This case affords interesting speculation with especial regard to pathogenesis. The combination of a slowly resolving pleural effusion on the right side accompanied with a complete collapse of the underlying lung together with a stationary nodule in the opposite lung suggests that the lesion at the left side was the older. The persistence of firm, well circumscribed lesions following an attack of coccidioidomycosis is well known. In this hospital 2 other patients had been observed with solitary parenchymal lesions persisting twelve to twenty-two months respectively following the acute infection. The patients remained asymptomatic for many months. From the roentgenologic standpoint both pathologic processes could be due to either tuberculosis or coccidioidomycosis. Colburn,[4] in a recent report of a series of seventy-five acute infections with coccidioidomycosis in soldiers, reported only 2 cases, or 2.7 per cent, in which there was massive pleural effusion. The effusion resolved slowly, and even after ninety days considerable pleural thickening remained. Neither of the 2 patients had a parenchymal lesion. An additional 10 per cent of these patients had mild and unusually localized pleural reactions. Colburn's division of his large group of patients into those primarily with patchy pneumonitis, with hilar adenitis and adenopathy, with pleural effusion, with cavitation or with a combination of these processes reflects the generally accepted classification arising not from coccidioidomycosis but from tuberculosis. From the roentgenologic changes alone, the two diseases in the majority of cases are similar.

Smith [3] made note of the fact that he had never seen a simple coccidioidal pleural effusion fail to absorb. Several persons, however, had been seen by him with a coccidioidal empyema, in 1 of whom it persisted for over one year. It has been impossible to obtain a complete history of our patient's first episode. It appears highly probable that this was a severe infection, since he was hospitalized for a period of six months. It is apparent that the onset of the spontaneous pneumothorax occurred while he was overseas. The exact nature of this incident remains obscure. It is possible that a subpleural tuberculous cavity had ruptured into the pleura, with a resultant bronchopleural fistula, and that during this process extension into a well localized and latent coccidioidal infection had occurred. It may well be, as Smith suggested, that a subpleural, coccidioidal cystlike cavity had ruptured and precipitated the trouble. The possibility of a cavity, in which both organisms had resided, which ruptured into the pleural cavity is remote but might be considered. There is nothing to indicate that there is a disseminated coc-

4. Colburn, J. R.: Roentgenological Types of Pulmonary Lesions in Primary Coccidioidomycosis, Am. J. Roentgenol. **51**:1-8 (Jan.) 1944.

cidioidal infection. The low sedimentation rate, the normal temperature and pulse, the absence of abnormal physical findings except in the chest, the progressive recovery of the patient, the absence of toxicity, the low titer of the complement fixation test and the negative precipitin reaction with undiluted antigen all point to the fact that this is not a progressive spreading infection but one which is essentially mechanical in nature.

SUMMARY

A case of a young soldier with coexisting active tuberculosis and coccidioidomycosis is presented. C. immitis and Myco. tuberculosis were both isolated from the pleural fluid by cultural methods and inoculation of a guinea pig.

Montefiore Hospital, Gun Hill Road, New York.

SEPTIC STAPHYLOCOCCEMIA SUCCESSFULLY TREATED BY PENICILLIN AND BACTERIOPHAGE

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NEW YORK

SEPTIC staphylococcemia, its complications and sequelae have been a major problem for study by our group for many years. Several papers have appeared from time to time dealing with the use of bacteriophages in many hundreds of patients and presenting in detail the therapeutic program in some of the more serious clinical varieties of this infection, such as osteomyelitis, septic thrombosis of the cavernous sinus, staphylococcic meningitis and staphylococcic endocarditis. The introduction of the sulfonamide drugs and subsequently of penicillin was followed by their enthusiastic use against staphylococcic infections, with success in many instances. More recently, streptomycin is being employed against the staphylococcus because of the well known but inadequately discussed failures in sulfonamide and penicillin therapy of infections with resistant staphylococci. At this time we wish to present the record of a patient with fulminant septic staphylococcemia, apparently complicated by localization on the endocardium and in the lumbar portion of the spine, in whom the infecting staphylococcus was remarkably resistant to penicillin and moderately resistant to bacteriophages in the culture tube. The patient was successfully treated by the use of these therapeutic agents in combination.

REPORT OF A CASE

S. D., a white woman aged 64, was admitted to the hospital on Dec. 31, 1944, with chills and fever which had begun on the previous day. The temperature on admission was 104.6 F., and clinical opinion favored a diagnosis of pneumonia, but roentgenologic examination revealed no evidence of gross pulmonary infiltration. There was an area of inflammation on the great toe of the left foot, about a large fissured corn, and this may have been the portal of entry for the infection.

The earlier part of her record at the hospital is shown in abridged form in the charts. Culture of the patient's blood taken on admission developed 13 colonies of Staphylococcus aureus per cubic centimeter of blood, and the succeeding cul-

Aided by grant no. 539 of the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

From the Department of Bacteriology and the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

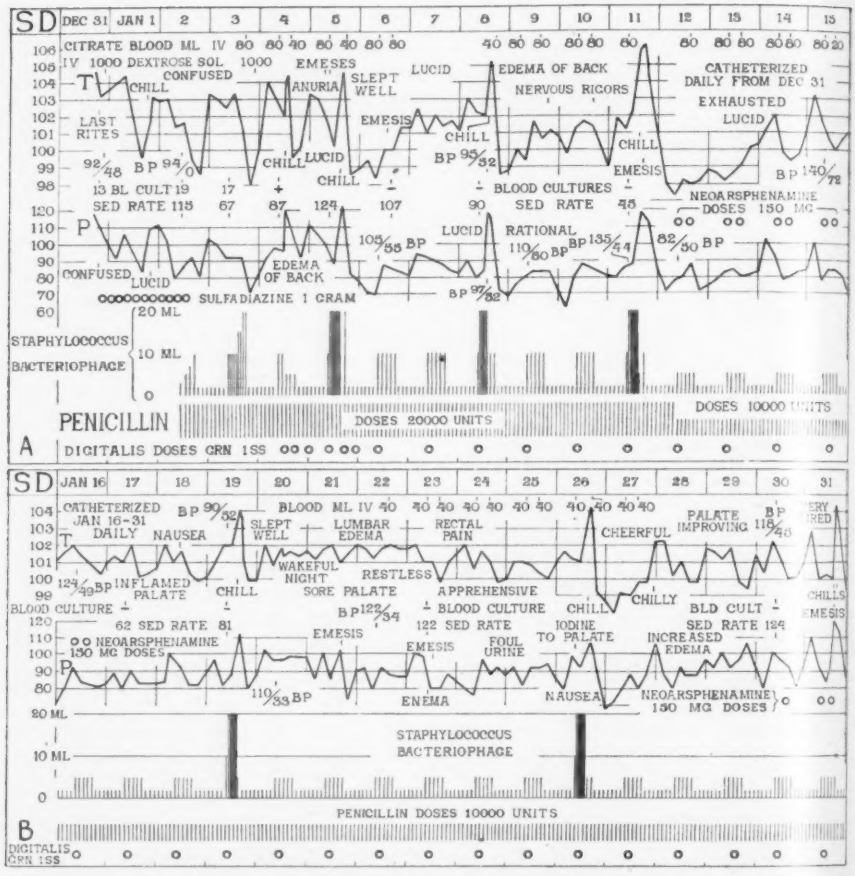
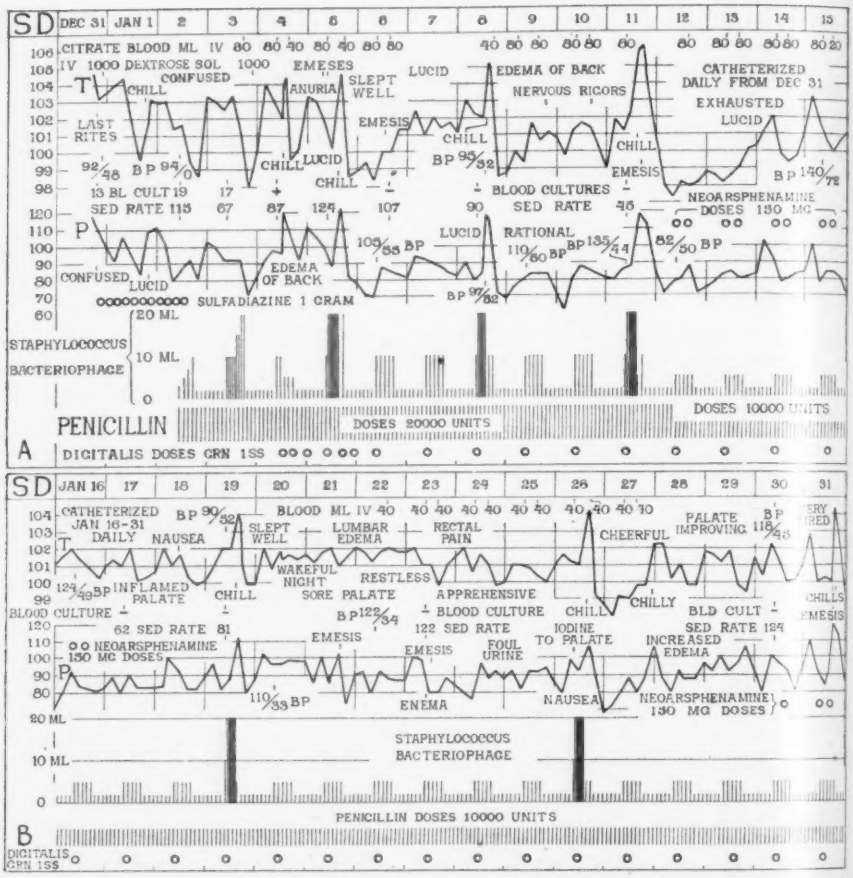


Chart 1.—*A*, abbreviated clinical record of S. D. from her admission, on Dec. 31, 1944, to Jan. 16, 1945. The extremely grave prognosis on admission was indicated by the high temperature, rapid pulse, low blood pressure and mental confusion. The first culture of the blood, taken on the evening of December 31, brought to development 13 colonies per cubic centimeter of the patient's blood, first recognized on the morning of January 2, at which time anti-infectious therapy for the staphylococcemia was initiated and the use of sulfadiazine discontinued. The culture of the blood taken on January 2 yielded 19 colonies per cubic centimeter of the patient's blood, that of January 3 yielded 17 and that of January 4 showed growth of less than 1 colony per cubic centimeter of blood. The subsequent cultures of the blood remained sterile. Blood was given by fractional transfusion, beginning with 80 cc. on the afternoon of January 3. It was necessary to catheterize daily. There was extensive edema over the lower region of the back after January 4. Penicillin dosage was 20,000 units every two hours given intravenously during the day and by intramuscular injection at night, from January 2 to January 12, and subsequently it was 10,000 units every two hours. Staphylococcus bacteriophage was given intravenously on January 2 in increasing doses of 3, 5, 7

and 10 cc., followed by the uniform doses of 2 cc. every two hours during the night. On January 3 another series of doses at intervals of approximately sixty minutes was given, 10, 10, 10, 10, 10, 15, 15, 20 and 20 cc., beginning at 9:30 a. m. and ending at 5:30 p. m., without recognized febrile reaction. However, the bacterial population of the blood stream was diminished in the next culture of the blood. On January 4 the two intravenous injections of 10 cc. of bacteriophage were followed by a definite chill shortly after midday. The behavior of the patient suggested a Hugh Young reaction, and the subsequent psychic improvement was in accord with this interpretation. On January 5 the doses of bacteriophage were pushed to higher levels, not precisely depicted on the chart: at 7:30 a. m., 2 cc.; 9:31 a. m., 10 cc.; 10:24 a. m., 20 cc.; 11:29 a. m., 30 cc. (heavy line); 12:30 p. m., 37 cc. (heavy line); 1:33 p. m., 50 cc. (heavy line); 2:31 p. m., 70 cc. (heavy line), and 5:29 p. m., 20 cc. On this day there was a typical Hugh Young reaction, beginning with chill at 3:15 p. m. and a rise in temperature to 104.6 F., with a subsequent rapid fall of temperature to 98.6 F. at 8 p. m. After two days of rest a shock reaction was again induced, on January 8, by another series of large doses of bacteriophage: at 7:30 a. m., 2 cc.; at 9:34 a. m., 10 cc.; at 10:35 a. m., 20 cc.; at 11:31 a. m., 30 cc. (heavy line); at 12:28 p. m., 40 cc. (heavy line); at 1:30 p. m., 30 cc. (heavy line); at 1:45 p. m., 20 cc. and at 3:37 p. m., 10 cc. Again there was a Hugh Young reaction, chill at 2 p. m., rise in temperature to 105.2 F. at 3:30 p. m. and diaphoresis and rapid decline of temperature to 98.6 F. at 8 p. m. Again on January 11 a series of increasing doses of bacteriophage was given: at 7:30 a. m., 2 cc.; 9:33 a. m., 10 cc.; 10:29 a. m., 20 cc.; 11:42 a. m., 30 cc. (heavy line); 12:50 p. m., 40 cc. (heavy line); 1:35 p. m., 50 cc. (heavy line); 2:39 p. m., 70 cc. (heavy line); 3:32 p. m., 5 cc. and 5:31 p. m., 10 cc. The Hugh Young reaction on this day was more severe, with chill, emesis, a rise in temperature to 106.2 F. and subsequent rapid decline to 97.4 F. at 8:00 a. m. on January 12. Neoarsphenamine in intravenous doses of 150 mg. was given twice daily on January 12, 13, 14, 15 and 16. The condition of the patient was still regarded as critical in the middle of January. The blood pressure reading of 140 systolic and 72 diastolic on January 15 was more satisfactory than the previously recorded figures. *B*, abbreviated clinical record of S. D. from Jan. 16 to 31, 1943. The cultures of the blood of January 17, 19, 23 and 30 remained sterile. The sedimentation rate remained abnormally high on all examinations. Use of a catheter had to be continued. There was also considerable difficulty with bowel elimination, and the colonic irrigation coupled with digital removal of impacted material on January 23 was followed by complaints of serious discomfort. Extensive inflammation of the roof of the mouth was an additional distressing complication, which finally responded to the application of tincture of iodine. On January 19 another intensive series of doses of bacteriophage was administered: at 7:30 a. m., 2 cc.; 9:31 a. m., 10 cc.; 10:30 a. m., 20 cc.; 11:32 a. m., 30 cc. (heavy line); 12:30 p. m., 50 cc. (heavy line); 1:30 p. m., 70 cc. (heavy line); 2:40 p. m., 50 cc. (heavy line); 3:30 p. m., 5 cc., and 5:30 p. m., 5 cc., followed by the usual intramuscular injection of 2 cc. beginning at 7:30 p. m. The Hugh Young reaction on this day was only moderately severe. On January 26 the intensive doses of bacteriophage were as follows: 7:30 a. m., 2 cc.; 9:32 a. m., 10 cc.; 10:34 a. m., 20 cc.; 11:30 a. m., 30 cc. (heavy line); 12:30 p. m., 50 cc. (heavy line); 1:32 p. m., 70 cc. (heavy line); 2:30 p. m., 100 cc. (heavy line); 3:29 p. m., 5 cc., and 5:31 p. m., 5 cc. On this day the temperature rose to 104.2 F. and it descended to 98.0 F. the next morning. Neoarsphenamine was again injected from January 30 to February 4. Administration of digitalis had been started on January 4, and maintenance doses were continued throughout the subsequent period covered by the charts. Toward the end of January the patient seemed to be losing ground, and on January 31 she had two distinct chills and a rise in temperature to 104.4 F., not clearly related to any therapeutic procedure.



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tures, taken on January 2, 3 and 4, developed the same microbe. Study of this staphylococcus disclosed that it was resistant to penicillin, so that even 500 units of penicillin per hundred cubic centimeters of broth failed to cause the slightest recognizable inhibition of growth in the test tube. It was also rather resistant to the available bacteriophages, so that even after many serial filtrations complete clearing of the culture was not observed and the maximum lytic effect was read as 2 plus at four hours and zero at twenty-four hours. Subsequent serial filtrations failed to maintain this effect. Nevertheless the treatment was undertaken, although without expectation of success. On January 2 the patient was still mentally confused, with occasional lucid intervals. Moderate apical and aortic systolic murmurs were heard, both of which were thought to be of recent origin. Penicillin, 20,000 units by intravenous injection during the day and by intramuscular injection at night, was given from 11:33 a. m. on January 2 to January 12, and it was given thereafter in doses of 10,000 units at the same intervals. Stock staphylococcus bacteriophage was regularly injected along with the peni-

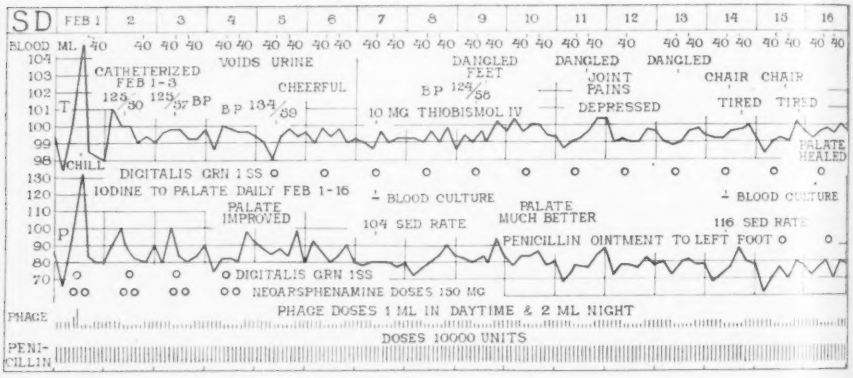

Chart 2.—Abbreviated clinical record of S. D. from Feb. 1 to 16, 1945. After the usual medication during the night of January 31, the dose of bacteriophage was decreased to only 3 cc. at 9:31 a. m. on February 1, followed by administration of 5 cc. at 11:35 a. m., along with the usual 10,000 units of penicillin at each injection. There was a chill beginning at 12:30 noon. Smaller doses of the bacteriophage were given thereafter. The small transfusions and the maintenance doses of digitalis were continued as indicated on the chart. Use of neoarsphenamine was discontinued after February 4. Urine was voided naturally after February 3. A single injection of thio-bismol was given on February 7 but not repeated. The intravenous administration of neoarsphenamine and thio-bismol served to supplement other anti-infectious therapy.

cillin but in varied doses, and on some days the bacteriophage was given every hour. The chart is not adequate in showing the details of dosage of bacteriophage but does give a general idea of it. The first dose of bacteriophage was 3 cc. injected intravenously along with the penicillin at 11:33 a. m. on January 2. This was followed at intervals of two hours by injections of 5, 7 and 10 cc. at 1:30, 3:32 and 5:30 p. m. respectively. Then, at 7:30 p. m. and on through the night, the dose of bacteriophage was 2 cc. given by intramuscular injection up to 7:30 a. m. inclusive. On January 3 the bacteriophage was given every hour in a dose of 10 cc. from 9:30 a. m. to 1:30 p. m. inclusive, making a total

of 50 cc. in the five doses. Then a dose of 15 cc. was given at 2:34 p. m. and repeated at 3:34 p. m., followed by 20 cc. at 4:43 and again 20 cc. at 5:32 p. m. In the eight hours from 9:30 a. m. to 5:32 p. m. she therefore received 120 cc. of bacteriophage intravenously. There was no evident reaction. Her mental condition cleared somewhat at about 3 p. m., and there was profuse diaphoresis and lowering of temperature in the evening. At this time an increasing subcutaneous edema was observed, especially over the lumbar region and the buttocks but also on the arms.

On January 4 the dose of bacteriophage at 9:31 a. m. was 10 cc., and this dose was repeated at 11:26 a. m. The patient went into a chill at 12:15 p. m., which lasted thirty minutes, and her temperature rose to 104.4 F. The dose of bacteriophage at 1:20 p. m. was reduced to 5 cc., and this was repeated at 3:31 p. m. and at 5:31 p. m., after which the usual injections of 2 cc. were given through the night. At 2:15 p. m. on this day 1,200 cc. of urine was taken by catheter, and, although some urine was voided naturally at times, catheterization was required daily during the period from December 31 to January 15. On January 5, after a delirious night, she was mentally clear. She vomited at 7:15 a. m. and again at 9:15 a. m. Bacteriophage was injected intravenously in increasing doses to produce a shock: 10 cc. at 9:29 a. m.; 20 cc. at 10:24 a. m.; 30 cc. at 11:29 a. m. (indicated by heavier line on chart 1 *a*); 37 cc. at 12:30 p. m.; 50 cc. at 1:33 p. m., and 70 cc. at 2:31 p. m., making a total of 217 cc. in about five hours. The chill started at 3:15 p. m. and terminated at 3:55 p. m., with an elevation of temperature to 104.6 F. at 4 p. m., followed by diaphoresis at 4:20 p. m. and sharp decline of temperature to 98.6 F. at 8 p. m. This appeared to be a fairly typical Hugh Young reaction and was regarded as encouraging. At 5:30 p. m., after an interval of three hours because of the chill, an injection of 20 cc. of bacteriophage was given along with the usual dose of penicillin and followed by administration of 40 cc. of citrated blood through the same needle. Subsequently the doses of bacteriophage were 2 cc. each during the night and 10 cc. each during the day, at intervals of two hours, until the morning of January 8. On this day, after blood had been taken for determination of the sedimentation rate and culture, an injection of 10 cc. of bacteriophage was given along with the penicillin at 9:34 a. m., followed by 20 cc. at 10:35 a. m.; 30 cc. at 11:31 a. m.; 40 cc. at 12:28 p. m.; 30 cc. at 1:30 p. m., and 20 cc. at 1:45 p. m. The dose of 50 cc. scheduled for 1:30 p. m. was partly withheld at that time because the patient said that she felt chilly, but when a genuine chill did not appear, the 20 cc. to complete the prescribed dose was administered at 1:45 p. m. At about 1:55 p. m. there was a definite chill, which lasted until 2:25 p. m., and at 3:10 p. m. the temperature reached 105.2 F. and then it descended to 98.6 F. at 8 p. m. The patient remained asleep, and there was profuse diaphoresis. The edema of the back persisted, but otherwise the patient seemed to be improved. The regular doses of bacteriophage, of 2 cc. during the night and 10 cc. during the day, were continued during January 9 and 10. On January 11 the doses of bacteriophage were stepped up to 10 cc. at 9:33 a. m.; 20 cc. at 10:29 a. m.; 30 cc. at 11:42 a. m. (represented by a heavier line in the chart); 40 cc. at 12:50 p. m.; 50 cc. at 1:35 p. m., and 70 cc. at 2:39 p. m.. The chill began at 2:45 p. m. and lasted fifty minutes. During the chill the patient was given an intravenous injection of 20,000 units of penicillin and 5 cc. of bacteriophage at 3:32 p. m. There was some mental confusion, and the temperature rose to 105.8 F. at 3:45 p. m. At 4:30 p. m. she vomited a large amount of undigested food and was incontinent. At 5:30 p. m. the temperature was 106.2 F., but nevertheless she was given an intra-

venous injection of 20,000 units of penicillin and 10 cc. of bacteriophage at this time. The patient remained semiconscious until about 10:30 p. m., at which time she began to sweat profusely and became mentally alert. This severe Hugh Young reaction exhausted her strength, but in other respects her condition seemed to be improved. The doses of bacteriophage were reduced to 5 cc. during the day and were continued at 2 cc. during the night, along with doses of penicillin reduced to 10,000 units every two hours. Neoarsphenamine, in doses of 150 mg., was given twice daily from January 12 to 16.

Chart 1 *B* shows the abridged record from January 16 to 31. Catheterization was still required during this period. An extensive inflammation of the palatal mucous membrane was a new and troublesome complication, which finally disappeared after frequent applications of tincture of iodine. Edema over the lumbar region persisted. Fractional transfusions, usually 40 cc. twice daily, were given from time to time. Cultures of the blood remained sterile, but the continued fever and the high sedimentation rate indicated persistent activity of the staphylococcic infection, probably on the valvular endocardium and possibly in other localizations not readily detected. On January 19 the doses of bacteriophage were again stepped up to induce a shock reaction: 10 cc. was given at 9:31 a. m.; 20 cc. at 10:30 a. m.; 30 cc. at 11:32 a. m.; 50 cc. at 12:30 p. m.; 70 cc. at 1:30 p. m., and 50 cc. at 2:40 p. m., making a total of 230 cc. of bacteriophage in approximately five hours. As the injection was being given at 2:40 p. m. the patient began to tremble and remarked that she was about to have a chill, and because of this the injection was limited to 50 cc. at this time. Actually she did go into a genuine chill, lasting thirty minutes, and her temperature rose to 104.0 F. at 4 p. m. Nevertheless she was given a small dose of 5 cc. of bacteriophage at 3:30 p. m. along with the penicillin. The Hugh Young reaction on this day was rather mild, and the patient was comfortable later in the evening. On January 23 there was a somewhat distressing fecal impaction, with consequent rectal trauma, which caused some apprehension. On January 26 another bacteriophage shock was induced. The doses of bacteriophage given intravenously were as follows: 10 cc. at 9:32 a. m.; 20 cc. at 10:34 a. m.; 30 cc. at 11:30 a. m.; 50 cc. at 12:30 p. m.; 70 cc. at 1:33 p. m., and 100 cc. at 2:30 p. m., making a total of 280 cc. of bacteriophage in five hours. The chill became distinctly evident at 3:15 p. m. and continued forty minutes, to 3:55 p. m. During this period of chilling, an intravenous injection of 5 cc. of bacteriophage and 10,000 units of penicillin was given at 3:29 p. m. The temperature rose to 104.2 F. at 4:30 p. m., and it descended promptly to 99.2 F. at 8 p. m. A restful night followed. The edema over the lumbar region and the buttocks increased, and the region was tender to pressure. The usual doses of bacteriophage and penicillin were given from January 27 to 31 inclusive. At 9:29 a. m. on January 30 the blood pressure reading was 118 systolic and 45 diastolic. On this day the patient was emotionally upset by war news concerning a son in the air service. Administration of neoarsphenamine in doses of 150 mg. twice daily was started again on the afternoon of January 30. From 3 to 5 a. m. on January 31 she complained of severe pain in the right thigh and leg, and in the morning she felt extremely tired after the restless night. However, she was cheerful during the day until 4:20 p. m., when she vomited and went into a chill, which lasted forty-five minutes, with a rise of temperature to 104.4 F. at 5:45 p. m. At 6:55 p. m. she had another chill, lasting ten minutes. These chills seemed to be without relation to any medication, and they may have been due to emboli. Nevertheless, because we had previously observed an increased sensitiveness to bacteriophage when

staphylococcemia was progressing favorably, it was decided to reduce the dose somewhat. Hence at 9:31 a. m. on February 1 the dose of bacteriophage was 3 cc., and at 11:35 it was again 5 cc. Curiously enough, the patient had chills again from 12:30 to 1 p. m., and her temperature rose to 104.8 F. at 1:30 p. m. It seemed that this reaction was induced by the smaller amounts of bacteriophage injected intravenously, namely 3 cc. at 9:31 a. m. and 5 cc. at 11:35 a. m. Therefore the subsequent doses of bacteriophage were at a lower level, 1 cc. intravenously every two hours in the daytime and 2 cc. by intramuscular injection every two hours at night. The doses of citrated blood, of digitalis, of neoarsphenamine and of penicillin are clearly indicated on the charts. There was decided improvement in the record after February 2, and the use of a catheter was discontinued on February 3. The inflammation of the mouth subsided, and it was entirely healed on February 16. The patient dangled her feet on February 9 and tried sitting in a chair on February 14.

The subsequent record at the hospital extends to June 16, 1945, and it seems unnecessary to present it in detail. From February 17 to February 22 the temperature did not exceed 100.0 F. at any observation. The injections of bacteriophage and penicillin were continued as before. The large corn on the plantar surface of the great toe of the left foot, which was thought to be the portal of infection, was treated by application of penicillin ointment daily, beginning on February 13. On February 20 this massive corn had separated, so that it was lifted off in one piece without any bleeding, leaving a smooth epidermal surface. On February 23 the patient was out of bed, sitting in a chair in the morning and again for a half hour in the afternoon. When sitting, she suffered pain in the lumbar region and at times also in the thighs and legs. At 6:15 p. m. there was a definite chill, which lasted thirty-five minutes, with a rise in temperature to 101.8 F. at 6:50 p. m. Culture of blood taken during the chill remained sterile. The temperature did not exceed 100.0 F. again until March 6. On February 26 the use of penicillin was discontinued and the dosage of bacteriophage reduced to 2 cc. twice daily. The patient was out of bed in a chair one or more times a day, and she walked a short distance. However, the effort seemed to cause more pain in the back and in the lower extremities, and early in March she became discouraged about trying to leave her bed. Because of the continued complaints of pain in the lumbar region and in the lower extremities, a roentgenologic study of the lumbar area of the spine was made on March 6, and this disclosed articular erosion and necrosis of the neighboring articular surface between the third and fourth lumbar vertebrae, along with advanced osteoarthritic changes in the thoracic region as well as the upper part of the lumbar region of the spine. It was not possible to decide whether or not there had been a recent complicating staphylococcic infection superimposed on the old structural alterations. On account of these findings it was decided to avoid excessive pressure and strain on the lumbar portion of the spine until a suitable supporting corset could be prepared. She was allowed to be about in a wheel chair in a reclining position with adequate support to avoid strain or pressure on the back. Use of digitalis, which had been taken since January 4, was discontinued on March 6.

The visit to the department of radiology on March 6 was followed by a period of slight fever, with maximum temperatures of 100.4 F. on the evening of March 6, 101.6 F. on March 7, 100.8 F. on March 8, 100.4 F. on March 11 and 100.8 F. on March 12. Subsequently there was no temperature observed higher than 100.2 F. from March 13 to April 7 inclusive. The intravenous injections of 2 cc. of bacteriophage twice a day were continued during this period. She was

up in a wheel chair daily and walked with assistance on some days. However, on April 8 the temperature rose to 101.0 F. at 6 p. m. She had been on the sun roof in a wheel chair from 1:15 to 3:15 that afternoon and remained out of bed until 5:45 p. m. Shortly thereafter she complained of severe pains in the right arm and right leg, and her pulse became irregular. Physical examination did not aid in understanding this episode, which may, nevertheless, have been related to overexertion. Again the temperature rose to 101.2 F. at midnight on April 12 and to 101.4 F. at 4 a. m. on April 13. An abdominal binder was applied shortly after midnight, and this seemed to relieve the intense lumbar discomfort.

There was another febrile period, beginning on April 17, with a temperature of 101.0 F. at midnight, followed by high points of 101.6 F. on April 18; 101.4 F. on April 19; 101.0 F. on April 20, and 100.4 F. on April 21, again associated with irregular pulse. At this time she was emotionally disturbed because of serious illness of a relative, concerning whom she had only fragmentary information. However, this would not seem to be a wholly satisfactory explanation of the elevated temperature.

On April 23 there was a disturbance of another kind. After a restful night and a comfortable day, during which she received her usual intravenous doses of 2 cc. of bacteriophage at 9:33 a. m. and at 3:33 p. m., the patient had a definite chill at 4:55 p. m., lasting until 5:30 p. m. At this time there was severe pain in the legs, arms and back of the neck. The temperature rose rather slowly, registering 101.6 F. at 4:55 p. m.; 102.2 F. at 5:30 p. m.; 103.0 F. at 6:35 p. m., and 104.0 F. at 8 p. m., and it descended to 101.6 F. at 10 p. m.; 100.3 F. at 10:30 p. m., and 98.6 F. at 4 a. m. on April 24. The patient slept well. On April 24 and 25 she appeared well as usual. Then on April 26 there was a repetition of the upset. The patient sat in a chair from 3:15 to 4:15 p. m. and received her afternoon injection of 2 cc. of bacteriophage at 3:32 p. m., followed by 40 cc. of citrated blood. At 4:15 p. m. she drank a little wine (40 cc.) The chill started at 4:55 p. m. and lasted until 5:30 p. m. The temperature rose to 102.0 F. at 5:30 p. m. and 103.0 F. at 7 p. m. and then descended to 101.8 F. at 8 p. m. and 99.8 F. at 11:40 p. m. Subsequently the patient slept well. April 27 was uneventful, although the patient received intravenous injections of 2 cc. of bacteriophage and 40 cc. of citrated blood at 9:29 a. m. and 3:34 p. m., as usual. On April 28, however, there was a chill from 12:40 to 1:30 p. m., with a rise of temperature to 102.0 F., and again at 5:20 to 6 p. m., with the temperature rising to 103.4 F. at 7 p. m. The patient slept well after 10 p. m. These disturbances may have been due to (1) increased sensitiveness to the bacteriophage, (2) pyrogenic agents in the bacteriophage used, (3) pyrogenic substances in the citrated blood, (4) changes in the course of the patient's infection or (5) other, unrecognized, factors. We are inclined to ascribe them to some fault in the bacteriophage used or to increased sensitivity of the patient.

From April 29 to May 11 the temperature rose above 100.0 F. only once, when it was recorded as 100.4 F., at 8 p. m. on May 6. During this time the dose of bacteriophage was 1 cc. twice daily. The patient was out of bed much of the time and seemed to be definitely convalescent. On May 12 there was severe pain in the arms and legs throughout the day, and the temperature rose to 101.6 F. at 8 p. m. On each of the following days from May 13 to May 22 inclusive, the highest temperatures observed were 101.4, 102.0, 101.8, 100.2, 100.6, 100.0, 99.8, 100.4, 100.0 and 100.4 F. respectively. During this period of ten days the patient was out of bed in a chair and walking short distances as she desired. She complained continually of pain in the lower limbs, and there was definite edema over the left lumbar region.

Apparently the lumbar region of the spine had not yet healed so as to afford adequate support without undue pressure on nerve structures, and there were some difficulties in adjusting the special supporting corset. On May 14 activity out of bed was restricted to thirty minutes daily, and on May 16 the dose of bacteriophage was further reduced to 0.5 cc. twice daily, and the use of the bacteriophage was discontinued altogether on May 18. After May 22 the recorded temperature did not again exceed 100.0 F. Restrictions on activity were gradually relaxed, so that by June 1 she was out of bed most of the day. On June 13 she was out of the hospital on pass from 1:45 to 5 p. m., and on June 16 she was discharged.

Cultures of the blood of this patient were made at intervals of a week or oftener from December 31 to June 13. The specimens of December 31 and January 2, 3 and 4 yielded the staphylococcus. All others were sterile. The sedimentation rate of the blood was also tested once a week, and it was always abnormally high. During the last two months in the hospital, the weekly examinations from April 11 to June 13 inclusive gave the following figures: 60, 100, 115, 87, 35, 78, no examination, 82, no examination and 55. These readings represent millimeters of sedimentation at sixty minutes (Westergren technic), for which the normal figure should not exceed 18 mm. There was therefore some apprehension in regard to a possible persistent low grade activity of infection in the lumbar vertebrae.

Since her discharge the patient has continued to improve. In June 1946 she reported steadily satisfactory progress, with almost complete recovery of her usual health. The supporting corset is still used, and the back is still weak, so that she usually carries a cane when walking out of doors. The feet have remained free from the bothersome callosities which formerly caused so much discomfort.

COMMENT

There has been presented an objective and somewhat detailed account of the care in the hospital from Dec. 31, 1944 to June 16, 1945 of a woman aged 64 years who had a long-standing disorder of the lower part of the vertebral column and associated callosities and deformity of the feet, complicated by an acute septic staphylococcemia, beginning on December 30, and apparently giving rise to staphylococcic endocarditis and staphylococcic osteoarthritis of the lumbar region of the spine. The staphylococcus isolated in cultures of the blood was remarkably resistant to penicillin in the culture tube and also fairly resistant to the available bacteriophages. After the therapeutic use of these two agents in combination the bacteria promptly disappeared from the blood stream, and after a prolonged period of continued treatment the internal metastatic localizations of the infection were brought to a state of arrest, an outcome which was wholly unexpected in the earlier days of this illness.

The remarkable synergistic action of bacteriophages in combination with penicillin has been observed by Himmelweit [1] in Fleming's laboratory at St. Mary's Hospital, London, England. The therapeutic value

1. Himmelweit, F.: Combined Action of Bacteriophage and Penicillin on Staphylococci, Lancet **2**:104-105 (July 28) 1945.

of such combined or conjoined action has been indicated in previous reports [2] from our own laboratory. S. D., in the case reported, presents an outstanding example of an infection in which the staphylococcus was resistant to penicillin and to bacteriophage as individual agents, and yet the conjoined therapy was followed by recovery.

There are many obscure details in the behavior of a patient with staphylococcemia. The use of penicillin alone does not ordinarily induce the chill and the rise and decline in temperature which characterize the Hugh Young [3] reaction. Possibly the penicillin acts to restrain or to inhibit growth of the bacteria without operating to increase phagocytosis or bacteriolysis to an appreciable degree. Other agents, such as the merbromin of Young and especially the bacteriophages, appear to alter the bacteria so that they are more rapidly taken up by phagocytic cells [4] and more rapidly disintegrated by bacteriolytic action, resulting in the Hugh Young reaction, which resembles the paroxysm of early tertian malaria. Undoubtedly there are other chills which occur in the course of septic disease which are even less well understood.

Giving citrated blood by the method of fractional transfusion [5] has been our method of choice in the treatment of septic conditions for many years. It is most acceptable to the patients and not too great a burden to the physician when intravenous medication with other agents is regularly given.

SUMMARY

1. A woman aged 64 years, with moderate chronic disability due to changes in the lower part of the thoracic and lumbar regions of the spine, spinal cord and lumbar nerves, complicated by acute septic staphylococcemia, apparent septic endocarditis and metastatic osteoarthritis of the lumbar vertebrae, has been successfully treated by injections of penicillin and staphylococcus bacteriophage.

2. The staphylococcus in this case was resistant to penicillin alone and moderately resistant to bacteriophage alone.

3. The patient was well and active in June 1946, some seventeen months after the last culture of the blood was positive for pyrogens and about twelve months after her discharge from the hospital.

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2. MacNeal, W. J.; Poindexter, C. A., and Marty, F. N.: Apparent Arrest of Staphylococcal Endocarditis, Am. Heart J. **29**:403-408 (March) 1945. MacNeal, W. J.; Filak, L., and Blevins, A.: Conjoined Action of Penicillin and Bacteriophages, J. Lab. & Clin. Med. **32**:974-981 (Sept.) 1946.

3. MacNeal, W. J.: Specific Therapeutic Shock—The Hugh Young Reaction, Arch. Surg. **43**:579-582 (Oct.) 1941.

4. MacNeal, W. J.; Frisbee, F. C., and Slavkin, A. E.: Mechanism of Bacteriophage Action in Staphylococcus Bacteremia, Proc. Soc. Exper. Biol. & Med. **30**:12-14 (Oct.) 1932.

5. MacNeal, W. J., and Straub Neil, M. E.: Fractional Transfusion, J. Lab. & Clin. Med. **22**:842-845 (May) 1937.

HEMOLYTIC STREPTOCOCCIC SORE THROAT

The Poststreptococcic State

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IT HAS been known for more than thirty years that recovery from hemolytic streptococcic infection of the respiratory tract is frequently complicated by the development during convalescence of a variety of disorders including fever, arthritis, carditis and nephritis.[1] These conditions are clearly not the result of a direct invasion of the remote tissues by streptococci present in the throat during the initial illness and may be regarded as "late nonsuppurative complications"[2] of hemolytic streptococcic disease. The importance of this concept has been emphasized by the increasing body of evidence which indicates that rheumatic fever is one of the late complications of infection by hemolytic streptococci.

Recent investigation has greatly increased the information available in regard to the bacteriology, immunology and natural history of streptococcic infection and its complications. In a series of papers[3] the

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The laboratories of the Department of Medicine, Stanford University School of Medicine, were made available to the commission for certain purposes.

This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

The cooperation and assistance of Col. T. E. Harwood Jr., Major James Blanton and Capt. Howard Coggeshall are gratefully acknowledged. The study was made possible by the devoted efforts of Elizabeth Randall, Viola Ferris, Loraine Kerr and Helen Rantz, who were responsible for the technical and secretarial work.

1. Escherich, T., and Schick, B.: Scharlach, Vienna, A. Holder, 1912.

2. Keefer, C. S.: The Late Nonsuppurative Disorders of Hemolytic Streptococcal Diseases, Texas State J. Med. **35**:457, 1939.

3. (*a*) Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcal and Nonstreptococcal Respiratory Disease: A Comparative Clinical Study, Arch. Int. Med. **78**:369 (Oct.) 1946. (*b*) Rantz, L. A.; Spink, W. W., and Bois-

(Footnotes continued on next page)

pertinent literature has been reviewed, and the clinical manifestations of the intial phase of acute sore throat caused by group A hemolytic streptococci as observed in military personnel have been described, as well as the suppurative and nonsuppurative complications that followed. The latter disorders were specifically considered in two papers [3d,e] in which it was stated that the development of rheumatic fever was invariably preceded by a hemolytic streptococcic infection of the respiratory tract. A nonarthritic poststreptococcic continuing disease, with or without electrocardiographic evidence of carditis, was also observed. The pathogenesis of these disorders was considered, and the possible importance of reinfection by new types of group A hemolytic streptococci was emphasized.

The suggestion was made that all the arthritic and nonarthritic nonsuppurative poststreptococcic syndromes be considered together and be regarded as manifestations of the "poststreptococcic state." It is the purpose of this paper to describe the continuing disease that followed sore throat caused by group A hemolytic streptococci and to characterize the "poststreptococcic state" in detail.

METHODS

All patients suffering from disease of the respiratory tract of any type were admitted to certain wards in the station hospital, where they were seen by one of us. A history was obtained, a physical examination performed and cultures of materials from the throat and nose made. Patients discovered, on clinical and bacteriologic grounds, to be suffering from infection by hemolytic streptococci were transferred to special wards, where a permanent trained nursing staff was maintained, which permitted the execution of therapeutic and other investigative programs. These patients were studied by means of a variety of laboratory procedures. Cultures were made repeatedly of materials from the nose and throat, and the isolated hemolytic streptococci were classified serologically by the precipitin technics of Lancefield.[4] Serial white blood cell counts, erythrocyte sedimentation rates (Westergren) and electrocardiograms were obtained. Each patient was studied for not less than three weeks and frequently for a longer period.

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vert, P. J.: Hemolytic Streptococcus Sore Throat: The Course of the Acute Disease, ibid. **79**:272 (March) 1947. (*c*) Spink, W. W.; Rantz, L. A.; Boisvert, P. J., and Coggeshall, H.: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract: An Evaluation in Tonsillitis, Nasopharyngitis, and Scarlet Fever, ibid. **77**:260 (March) 1946. (*d*) Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, ibid. **76**:131 (Sept.) 1945. (*e*) Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Abnormalities in the Electrocardiogram Following Hemolytic Streptococcus Sore Throat, ibid. **77**:66 (Jan.) 1946. (*f*) Rantz, L. A.; Rantz, H. H.; Spink, W. W., and Boisvert, P. J.: Streptococcic and Nonstreptococcic Diseases of the Respiratory Tract: Epidemiological Observations, ibid. **77**:121 (Feb.) 1946.

4. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251.

THE CLINICAL MATERIAL

The nature of the group studied has been described elsewhere.[5] In brief, examples of sore throat caused by group A hemolytic streptococci, with and without rash, occurring in military personnel were intensively studied. Sixty-nine cases of this disease were selected in the previous analysis [3d] as possible examples of poststreptococcic nonsuppurative continuing disease. The criteria used for the differentiation of these cases were the presence of arthritis, electrocardiographic evidence of carditis or an erythrocyte sedimentation rate greater than 20 mm. per hour three weeks after the onset of the acute respiratory disease. Prolonged disability on the basis of definite local suppuration in the form of peritonsillar abscess, otitis media or paranasal sinusitis was observed in 15 additional men, who were excluded from consideration.

All the information obtained from the study of these examples of hemolytic streptococcic sore throat has been recorded on charts and exhaustively reanalyzed. As a result, certain cases which were disregarded have been included with the examples of nonsuppurative disease. Fifteen cases in which the erythrocyte sedimentation rate was persistently elevated were transferred to the group of suppurative complications, since sinusitis was probably present.[3b]

Complete detailed observations were available in 299 cases. Serial electrocardiograms were obtained in 185. The erythrocyte sedimentation rate at the end of three weeks was greater than 20 mm. per hour in 85. Local suppuration was definitely or probably responsible for the prolonged reaction of the tissue in 30 of these cases.

Seventy-two cases remained [5a] as possible examples of poststreptococcic nonsuppurative continuing disease on the basis of persistent unexplained abnormalities of the erythrocyte sedimentation rate or because of other clinical manifestations of illness.

CLINICAL OBSERVATIONS

Arthritis.—The course in 19 cases of hemolytic streptococcic sore throat was complicated by the development of arthritis. Fifteen of the patients, who were hospitalized as having typical examples of acute rheumatic fever, have been previously described.[3d] The cases of 4 additional patients, in whom the symptoms in the joints were less severe and who received ambulatory treatment, are included in this report. The essential clinical and laboratory data are presented in table 1. Cases 6 and 10 were described and illustrated elsewhere.[3d]

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5. Rantz, Boisvert and Spink.[3a,d] Rantz, Rantz, Spink and Boisvert.[3f]

5a. Infection by group A hemolytic streptococci was positively established in all these cases by the presence of rash or a significant antistreptolysin or antifibrinolysin response.

TABLE 1.—*Poststreptococcic Arthritis: Clinical and Laboratory Data*

Case No.	Infecting Type	Day of Onset of Arthritis	Duration of Arthritis, Days	Late Fever: Day of Onset	Late Fever: Duration, Days	Late Fever: Maximum Temperature, F.	Erythrocyte Sedimentation Rate *: First	Second	Third	Most Rapid Rate	Day First Normal	Electrocardiogram: Day First Done	Day First Abnormal	Duration of Abnormality, Days	Key No.†	Severity of Arthritis	Comment
1	Untypable	3	18	3	18	102.0	Not done	41/10	110/20	110/20	70 ‡	8	14	10	23	Severe	
2	46	17	7	16	9	104.0	26/2	10/ 9	100/20	111/24	48	19	19	12	25	Moderate	
3	36	15	5	13	11	103.0	35/2	22/12	97/19	97/19	44	8	Normal	Normal	..	Severe	
4	30, 36 and 19	63	16	63	5	102.0	48/2	92/26	38/36	106/70	90	36	36	50	26	Severe	Clinical reinfection
5	6 and 19	16	11	19	6	101.0	59/4	19/12	90/20	102/23	48	20	Normal	Normal	..	Severe	Inapparent reinfection
6	19	14	10	22	25	102.0	55/2	30/ 9	28/22	104/29	67	9	9	150	30	Severe	Pericarditis, days 25 to 65
7	30	16	4	12	8	103.0	8/2	30/ 7	57/13	90/19	40	7	7	35	28	Minimal	Complete heart block
8	19 and 3	39	11	39	9	102.0	Not done	Not done	46/35	103/51	90	44	44	8	29	Severe	Clinical reinfection; relapse of rheumatic fever on day 110
9	Untypable	35	10	35	3	99.0	Not done	Not done	37/18	93/38	50	36	36	45	31	Severe	
10	3, 46 and 30	38	10	36	8	105.0	14/2	6/18	9/30	75/41	71	9	Normal	Normal	..	Severe	Two clinical reinfections
11	3 and 1	42	8	40	2	100.0	12/3	4/ 9	3/22	27/41	49	9	Normal	Normal	..	Moderate	Inapparent reinfection
12	19	28	35	Afebrile	Afebrile	98.6	41/3	38/10	29/22	94/32	67	12	Normal	Normal	..	Moderate	
13	3	20	20	Afebrile	Afebrile	98.6	66/3	93/11	31/28	31/28	40	18	Normal	Normal	..	Minimal	Relapse of rheumatic fever on day 72
14	36	2	65	Afebrile	Afebrile	98.6	94/4	Not done	44/23	44/23	90	10	10	10	27	Mild	
15	26	20	14 ‡	Afebrile	Afebrile	98.6	29/3	31/ 9	37/22	37/22	44	9	Normal	Normal	..	Mild	Soles sore
16	36	12	9	Afebrile	Afebrile	98.6	70/2	Not done	42/23	42/23	39	38	38	7	21	Mild	Ankles, knees, elbows and shoulders painful
17	36	15	14	Afebrile	Afebrile	98.6	12/3	11/19	33/26	33/26	34	36	Normal	Normal	..	Mild	Knees and right elbow painful and swollen
18	36	19	14	Afebrile	Afebrile	98.6	42/2	9/ 8	43/19	43/19	34	34	Normal	Normal	..	Minimal	Pain in shoulder, elbow and wrist
19	36	25	14	22	17 ‡	99.4	32/3	27/ 8	36/22	39/39	39	Not done	Not done	Not done	..	Mild	Aching in knees and elbows

* Numerator is erythrocyte sedimentation rate, denominator is day following onset of streptococcic infection on which test was done.
† Refers to number of the case under which electrocardiograms were described in a previous paper.[3e]
‡ Last day of clinical observation.

The joints were first involved from three to sixty-three days after the onset of the acute streptococcic sore throat. A rise in temperature usually preceded this event by one to three days if fever was to be associated with the arthritic disease. Seven patients remained afebrile. The maximum temperature of the other patients varied from 99.0 to 105.0 F. but was less than 101.0 F. in only 2. Arthritis was regarded as severe in 8, moderately severe in 3, mild in 5 and minimal in 2 cases. An elevated temperature persisted during the arthritic illness for two to twenty-five days and was usually terminated by the administration of salicylates.

The erythrocyte sedimentation rate was abnormally rapid in every case during the arthritic phase of the disease. The maximum rates varied from 27 to 110 mm. per hour and were usually attained a few days after the involvement of the joints had become manifest. If the duration of abnormality of the erythrocyte sedimentation rate is determined in relationship to the initial streptococcic infection, it is discovered that the first normal rate was recorded after thirty days in no patients, after sixty days in 12 and after ninety days in the remainder. Recovery, as estimated by this test, occurred in 5 cases within forty days.

Electrocardiographic evidence of carditis was obtained in 9 of these cases. The nature and duration of the abnormalities observed have been previously described,[3e] and certain of these data are recapitulated in the table. The development of valvular cardiac disease was not recognized in any of these men during the period of study. Transient apical systolic murmurs were heard in several. Gallop rhythm in 1 and heart block in another patient were definite clinical signs of myocarditis. Persistent pericarditis was observed in a third patient.

In a previous paper [3d] it was noted that a true "latent" or quiescent period, separating the initiating streptococcic infection from the arthritic complication, was only occasionally observed in these cases. Abnormal electrocardiograms were present days to weeks before the onset of arthritis. The erythrocyte sedimentation rate remained abnormally rapid or increased during this intermediate period in 9 and came or remained within normal limits in 6 cases. Two were inadequately studied, and arthritis developed in 2 within three days of the onset of the initial streptococcic infection. Malaise was present during the "latent period" in several cases in which abnormal erythrocyte sedimentation rates were demonstrated during this interval.

No serologic type of hemolytic streptococcus was more likely than any other to incite the development of arthritis, since types 19, 30 and 36, which appear most frequently as the cause of the initiating infection in these cases, were also among the common types isolated in all cases of streptococcic disease in the station in which the study was made.[3f]

It may be of importance to record the fact that arthritis never followed monotype infections by the common type 17 (18 cases) or a food-borne epidemic strain of type 1 (over 250 cases).[6]

The importance of reinfection by new serologic types of hemolytic streptococci in the pathogenesis of the arthritic poststreptococcic state has been previously suggested.[3d] To recapitulate, bacteriologic or bacteriologic and clinical evidence of such reinfection was obtained in 5 of these cases, 3 of which were those in which a definite latent period occurred. It should also be noted that 75 men who were in various stages of convalescence from hemolytic streptococcic sore throat were exposed to reinfection by a type 1 Streptococcus during a food-borne

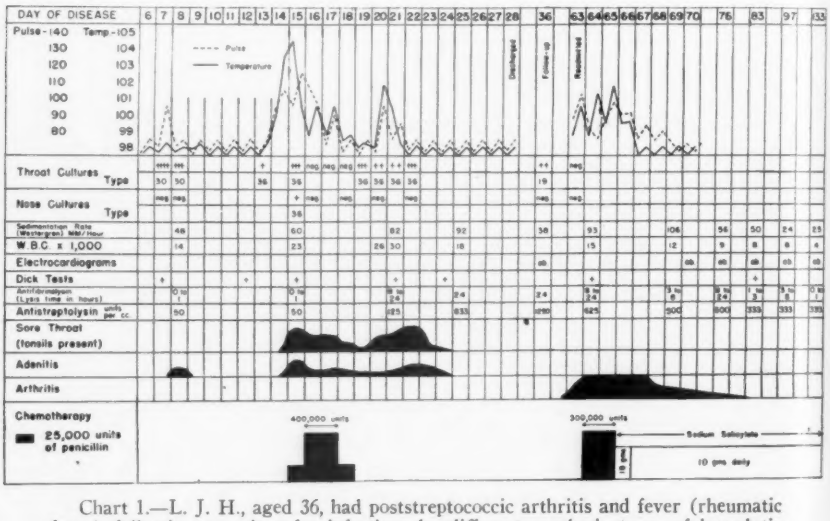

Chart 1.—L. J. H., aged 36, had poststreptococcic arthritis and fever (rheumatic fever) following a series of reinfections by different serologic types of hemolytic streptococci. There was no previous rheumatic fever.

epidemic, and a number showed definite laboratory and/or clinical evidence of invasion of the tissue by this organism. Arthritis developed in 3 of these men. This is approximately the same frequency of occurrence of involvement of the joints as that observed for the whole group.

Clinical summaries and charts of the course in 2 cases are appended, since each presents features of great interest.

CASE 4 (chart 1).—A 36 year old man was admitted to the hospital on the sixth day of a mild respiratory illness. The erythrocyte sedimentation rate and

6. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Hemolytic Streptococcus Sore Throat: Simultaneous Infection of a Large Number of Men by a Single Type, Arch. Int. Med. **76**:278 (Nov.-Dec.) 1945.

leukocyte count were elevated, and large numbers of type 30 hemolytic streptococci were recovered from the pharynx. Eight days later he suffered a reinfection by streptococci of type 36. This illness was inadequately treated with penicillin, and clinical and bacteriologic relapse occurred. He was clinically well by the twenty-seventh day and was discharged from the hospital, although the erythrocyte sedimentation rate and leukocyte counts remained abnormally elevated. When he returned for a follow-up examination on the thirty-sixth day, he was well but the erythrocyte sedimentation rate was 38 mm. per hour and the electrocardiogram abnormal (case 26 [3e]). Type 19 streptococci were present in the throat at this time. Twenty-seven days later he returned to the hospital febrile and with severe arthritis of the knees and elbows. The erythrocyte sedimentation

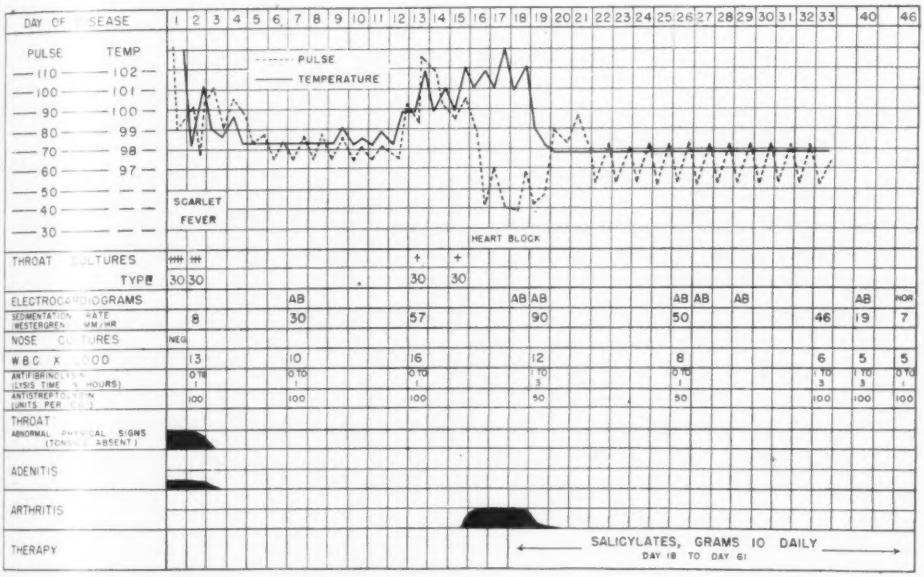

Chart 2.—Poststreptococcic arthritis, fever and complete heart block were seen in G. M. McC., aged 19.

rate had become more rapid, but the electrocardiogram presented abnormalities similar to those observed earlier.

The course of the disease was that of a severe attack of rheumatic fever, and he was not completely recovered on the one hundred and thirty-third day of the disease.

Comment.—This case illustrates the course of events in a man who suffered a clinical and also an inapparent reinfection by hemolytic streptococci of types different from those causing the initial illness. A true latent period was not established, and an abnormal erythrocyte sedimentation rate and electrocardiogram were discovered sixteen days after the last acute sore throat and twenty days before the appearance of arthritis.

Case 7 (chart 2).—A 19 year old youth was admitted to the hospital on the first day of a moderately severe infection by type 30 hemolytic streptococci.

A cutaneous rash was present. He made an uneventful recovery, but the erythrocyte sedimentation rate, which had been normal on admission, became progressively more rapid over the next twelve days. An electrocardiogram (case 28 [3a]) on the seventh day was abnormal, the T waves being flat in lead I and inverted in leads II and III. High temperature appeared on the twelfth day. Four days later, the pulse rate fell sharply, and complete heart block was demonstrated by electrocardiography. Minimal arthritis of the shoulders and hips was also noted at this time. The erythrocyte sedimentation rate was then 90 mm. per hour. After institution of salicylate therapy, the course was that of moderately severe rheumatic fever, and he had recovered by the forty-sixth day. Neither an antistreptolysin nor an antifibrinolysin response occurred.

Comment.—An initial streptococcic infection with rash (scarlet fever) was followed by a progressive increase in the reaction of the tissue as measured by the erythrocyte sedimentation rate. The electrocardiogram was abnormal on the seventh day. Five days later, poststreptococcic fever developed, followed in four days by the appearance of minimal arthritis and complete heart block. A true "latent period" was entirely absent.

Summary.—Hemolytic streptococcic sore throat was followed in 19 cases by the appearance of arthritis of varying degrees of severity. Fever was often associated with this complication. The erythrocyte sedimentation rate was invariably elevated during the arthritic phase of the illness and remained so for more than thirty days in every case. Abnormal electrocardiograms, indicating the presence of carditis, were discovered in 9 cases, in 3 of which there was also clinical evidence of myocardial involvement. Definite signs of permanent damage to the valves of the heart were not obtained during the period of study. Evidence of a continuing reaction of the tissue in the form of abnormal erythrocyte sedimentation rates and electrocardiograms was usually present during the "latent period," separating the acute suppurative illness from the arthritic phase of the disease.

LATE FEVER

The convalescence of 14 patients with hemolytic streptococcic sore throat was complicated by a recrudescence of fever. The essential data derived from a study of these men are presented in table 2. This event occurred after a period of normal temperature from five to nineteen days in length. Careful study failed to disclose a suppurative complication in any case as an explanation for the late elevation in temperature.

The maximum poststreptococcic temperature varied from 100 F. to 104 F. but was less than 101 F. in 6 of 11 cases in which detailed records of the temperature were available. An elevated temperature persisted for from two to more than forty days. Neither antibacterial nor salicylate chemotherapy was instituted in any case, since it was desirable to study the unaltered natural history of the illness.

The erythrocyte sedimentation rate was abnormally rapid during the period of late fever in 13 cases and remained so for more than twenty

TABLE 2.—*Poststreptococcic Fever: Clinical and Laboratory Data*

Case No.	Infecting Type	Late Fever: Day of Onset	Late Fever: Duration	Late Fever: Maximum Temperature, F.	Erythrocyte Sedimentation Rate *: First	Second	Third	Rate During Fever	Day First Normal	Electrocardiogram: Day First Done	Day First Abnormal	Duration of Abnormality, Days	Key No.†	Comment
20	36	5	2	101.0	14/2	89/8	11/21	89/8	21	8	Normal	Normal	..	
21	19, 28 and untypable	9	9	100.0	30/2	25/8	20/21	29/14	30	8	8	Over 24	16	Illustrated in text
22	19 and 36	12	28	100.0	52/4	59/15	68/29	68/29	50	15	Normal	Normal	..	Illustrated in text
23	17	6	7	101.5	41/2	87/8	32/20	90/14	29	7	7	7	..	Illustrated in text
24	46	6	12	100.0	50/2	73/8	18/20	73/8	20	8	Normal	Normal	..	
25‡	36	19	7	102.0	....	....	.....	.....	..	..	..	..	9	Illustrated in teext
26	30	15	5	100.0	17/2	3/8	48/21	48/21	Over 21	Not done	Not done	Not done	..	
27	26	10	4	101.0	12/3	10/9	10/22	7/14	Unknown	9	Normal	Normal	..	
28	19	13	8	99.8	40/3	25/8	35/24	27/19	Over 24	14	Normal	Normal	..	
29	19	10	Over 40	100.0	44/2	63/9	72/21	87/17	Over 68	12	Normal	Normal	..	Illustrated in text
30	19	Unknown		99.6	17/3	44/8	25/33	25/33	Over 33	10	Normal	Normal	..	Fever discovered in outpatient follow-up
31	3	6	2	104.0	45/2	32/8	15/21	32/8	21	8	8	Over 14	12	
32	30 and 1	Unknown		100.0	33/2	1/13	37/21	44/33	Over 33	13	13	Over 20	10	Fever discovered in outpatient follow-up
33	30, untypable and 26	Unknown		100.0	27/3	15/9	25/53	35/44	Over 44	9	25	Under 19	17	Fever discovered in outpatient follow-up

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which test was done.

† Refers to number of the case under which electrocardiograms were described in a previous paper.[3e]

‡ Data on this case is given in the text.

days in all, for more than thirty days in 5 and for more than forty days in 3 cases.

Serial electrocardiograms were obtained for 13 of these patients, and evidence of carditis was discovered in 5. The abnormalities were similar to those that were observed during arthritic poststreptococcic disease but were not so pronounced, nor were they as persistent. Clinical signs of carditis were not discovered, nor was permanent cardiac valvular disease diagnosed in any of these cases during the relatively brief period available for continued observation.

Malaise was severe in most of these men during the late febrile illness, and it frequently continued after the temperature had returned to normal.

Evidence of continuing reaction of the tissue in the form of an elevated erythrocyte sedimentation rate was demonstrable during the afebrile intermediate period in 2 of the 4 cases in which the late fever appeared fourteen days after the onset of the initial streptococcic disease. In the others, the interpretation of observations during the "latent period" was impossible because fever reappeared so quickly after the termination of the initial illness.

No single serologic type of hemolytic streptococcus predominated as the etiologic agent in the initial streptococcic infection preceding the development of late fever. Bacteriologic or bacteriologic and clinical evidence of reinfection by a new type was obtained in 4 cases.

Five of these examples of poststreptococcic fever will now be illustrated and described.

CASE 21 (chart 3).—A 19 year old youth was admitted to the hospital on the first day of a severe sore throat caused by type 19 hemolytic streptococci. The erythrocyte sedimentation rate was 30 mm. per hour and the leukocyte count 15,000 per cubic millimeter. He reacted positively to the Dick test, but no rash was observed. His reaction to the Dick test had become negative by the twenty-ninth day. He recovered uneventfully, but there was a recurrence of fever associated with a recrudescence of cervical adenitis on the ninth day, which persisted for twelve days. During this time he felt ill, and headache was severe. There was no clinical evidence of sinusitis, and roentgenograms of the chest were normal. The erythrocyte sedimentation rate remained moderately elevated, and the electrocardiograms (case 16 [3e]) obtained on the eighth day and later were abnormal. Type 28 streptococci had become the predominant flora of the nose and throat by the twenty-eighth day.

He was discharged from the hospital before complete recovery had occurred. Another febrile episode began on the twenty-ninth day, and he was readmitted to the hospital. Untypable streptococci were now present in large numbers, but there was no clinical evidence of a new suppurative lesion in the throat. A diffuse macular rash was noted over the trunk, but no Koplik spots appeared. The erythrocyte sedimentation rate was not decidedly elevated, but the electrocardiogram was still abnormal. The temperature returned to normal, and he was discharged. No further follow-up was possible.

Comment.—An example of late fever with carditis and cervical adenitis, appearing five days after the termination of the initial suppurative phase of acute hemolytic streptococcic sore throat is illustrated by this case. This episode may have been related to a reinfection by a new type of Streptococcus. Fever reappeared later, in association with a rash, and another type of Streptococcus was isolated from the throat. The exact nature of the latter process could not be ascertained.

CASE 22 (chart 4).—A 25 year old man was admitted to the hospital on the second day of a severe sore throat caused by type 36 hemolytic streptococci. He received 30 Gm. of sulfadiazine in six days and improved over a five day period, but withdrawal of the drug was followed by a clinical relapse, with recrudescence of the abnormal physical signs in the throat and neck and return of fever. The erythrocyte sedimentation rate and leukocyte count remained elevated for two weeks but were falling on the twenty-third day, at which time he felt well. Type 19 streptococci had become the predominant organisms four days later in the flora of the throat and nose. A notable increase in the erythrocyte sedimentation rate, which persisted until the fifteenth day, was closely associated with this event. The electrocardiogram was normal on three occasions.

Low grade fever was present from the twelfth to the forty-third days, when he was transferred to a convalescent barracks. He felt well until the twenty-ninth day, when easy fatigability followed by loss of weight was noted. Physical examinations and roentgenograms of the chest revealed nothing remarkable.

Full clinical recovery, with return of a sense of well-being, did not occur until the fifty-fifth day, at which time the erythrocyte sedimentation rate was still 19 mm. per hour. Fifty days later, he was well and the physical examination revealed no cardiac or other abnormalities.

Comment.—Sore throat caused by type 36 hemolytic streptococci was complicated by relapse following the withdrawal of administration of sulfadiazine and an inapparent reinfection by type 19 streptococci. The latter event was followed by a prolonged period of disability associated with low grade fever, malaise, loss of weight and a rapid erythrocyte sedimentation rate. Complete recovery did not occur until the fifty-fifth day of the illness.

CASE 23 (chart 5).—A 35 year old man was admitted to the hospital on the first day of a severe sore throat caused by type 17 hemolytic streptococci. He was afebrile by the fourth day, and he appeared to be recovering. A sharp rise in temperature associated with a decided increase in malaise occurred on the sixth day. No abnormalities were discovered on the physical examination to explain this event. A definite increase in the erythrocyte sedimentation rate and leukocyte count was discovered, and serial electrocardiograms revealed a transient inversion of the T wave in lead III. He was afebrile by the thirteenth day, but complete recovery, with return of the erythrocyte sedimentation rate to normal, did not occur until the fourth week of illness.

Comment.—The condition in case 23 is an example of poststreptococcic fever of seven days' duration, beginning on the sixth day and not explained by extension of the suppurative process. There was an increase in the erythrocyte sedimentation rate and leukocyte count and questionable transient electrocardiographic evidence of carditis.

CASE 25 (chart 6).—A 24 year old man was admitted to the hospital on the first day of a moderately severe sore throat caused by type 36 hemolytic streptococci, from which he recovered rapidly and uneventfully, the erythrocyte sedimen-

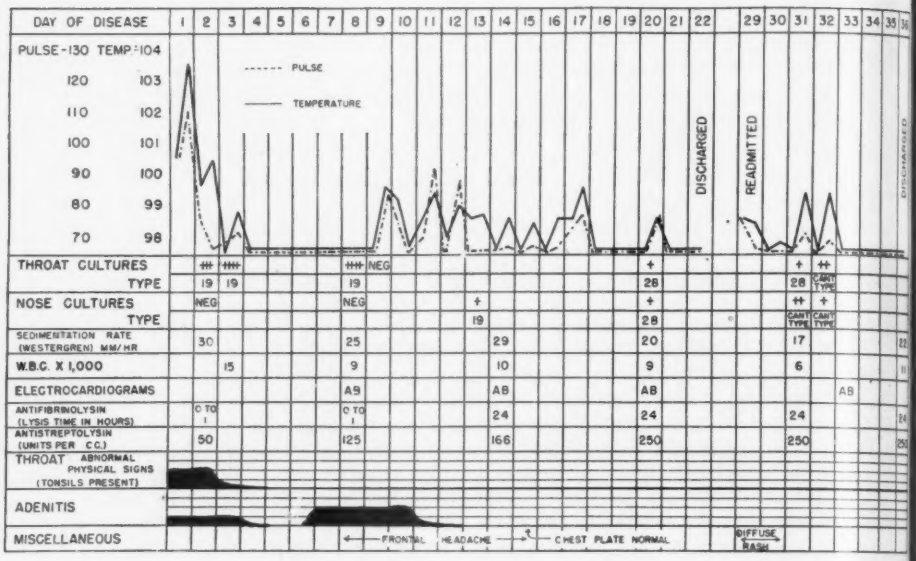

Chart 3.—Two episodes of poststreptococcic fever associated with carditis were observed in E. G. C., aged 19.

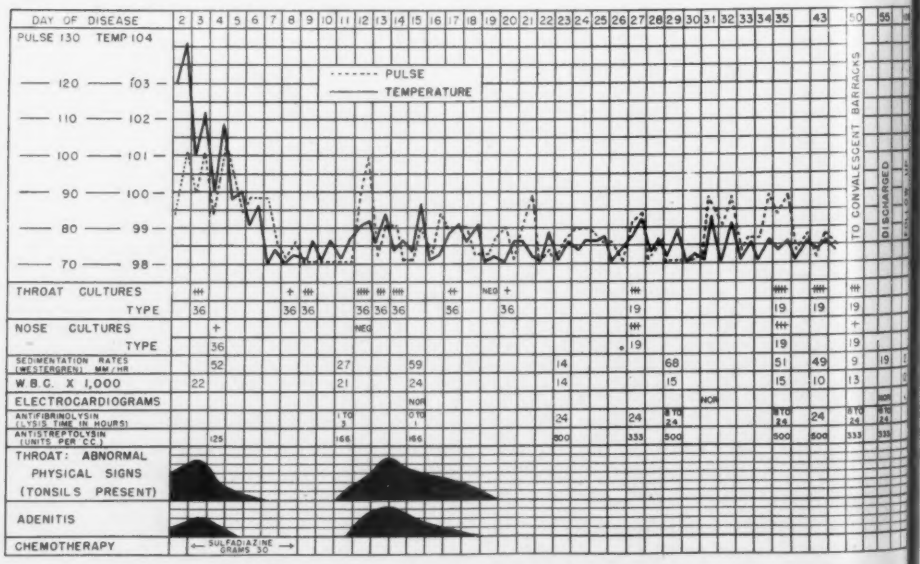

Chart 4.—Prolonged low grade poststreptococcic fever, malaise and persistently elevated erythrocyte sedimentation rate were evidenced by P. H., aged 25.

tation rate being 6 mm. per hour on the tenth day. Headache, anorexia and fever appeared on the eighteenth day, and he reentered the hospital. The erythrocyte sedimentation rate was abnormally rapid, and an electrocardiogram revealed the presence of a decidedly prolonged P-R interval (case 9 [8e]). His fever abated on the twenty-sixth day, and he was discharged although the erythrocyte sedimentation rate had increased. Three days later another febrile episode occurred, and he again was admitted to the hospital. The erythrocyte sedimentation rate was still abnormal, and the degree of heart block increased. He promptly became afebrile, but moderate tachycardia persisted. He was discharged, against advice, and returned to work. When seen in follow-up on the forty-third day he felt well, but

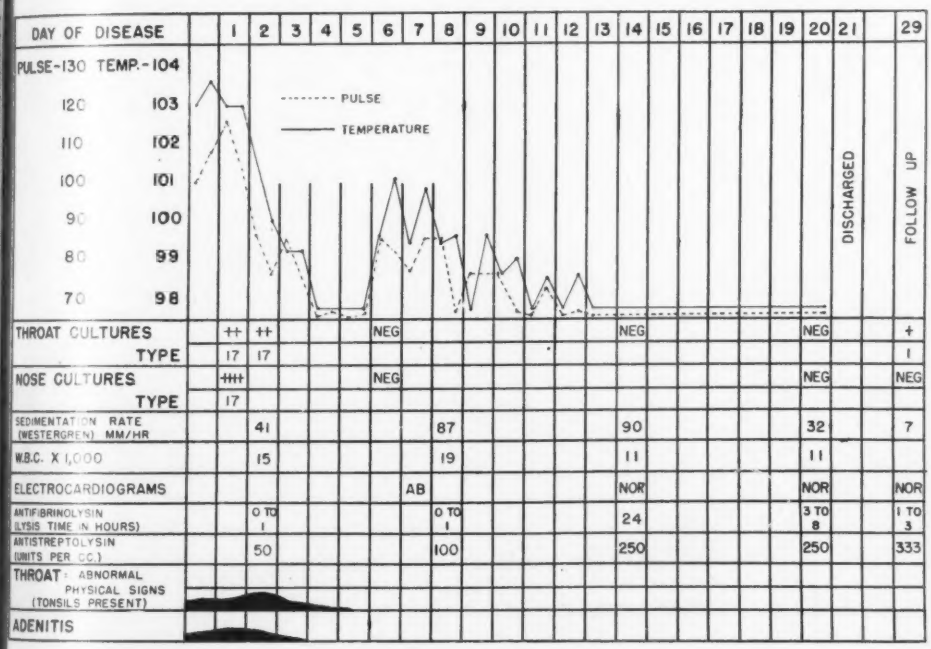
DAY OF DISEASE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 29
PULSE-130 TEMP.-104
120 103
110 102
100 101
90 100
80 99
70 98
PULSE
TEMPERATURE
DISCHARGED
FOLLOW UP
THROAT CULTURES ++ ++ NEG NEG NEG +
TYPE 17 17 1
NOSE CULTURES +++ NEG NEG NEG
TYPE 17
SEDIMENTATION RATE (WESTERGREN) MM/HR 41 87 90 32 7
W.B.C. X 1,000 15 19 11 11
ELECTROCARDIOGRAMS AB NOR NOR NOR
ANTIFIBRINOLYSIN (LYSIS TIME IN HOURS) 0 TO 1 0 TO 1 24 3 TO 8 1 TO 3
ANTISTREPTOLYSIN (UNITS PER CC.) 50 100 250 250 333
THROAT: ABNORMAL PHYSICAL SIGNS (TONSILS PRESENT)
ADENITIS

Chart 5.—Poststreptococcic fever, with minimal evidence of carditis, was observed in W. E. G., aged 35.

the erythrocyte sedimentation rate was 20 mm. per hour and the P-R interval prolonged.

Comment.—This is a case in which a monotype infection was followed by a true latent period. Later, two episodes of poststreptococcic fever associated with carditis supervened. Complete recovery had not occurred by the forty-third day.

Case 29 (chart 7).—A 34 year old man was admitted to the hospital on the first day of a moderately severe sore throat caused by type 19 hemolytic streptococci, from which he recovered uneventfully after the administration of 400,000 units of penicillin in thirty-two hours. He was approximately afebrile by the fourth day, and he remained so for five days. During this time the leukocyte count fell

to 10,000 per cubic millimeter. On the ninth day low grade fever appeared, and it continued until the patient's discharge. Simultaneously, the erythrocyte sedimentation rate was discovered to have become more rapid, and leukocytosis had recurred.

He was transferred to a convalescent barracks and was seen in follow-up on the seventeenth day, when he was febrile and the erythrocyte sedimentation rate was extremely rapid. He had become afebrile by the twenty-first day, and by the twenty-sixth day the erythrocyte sedimentation rate had become slower but was

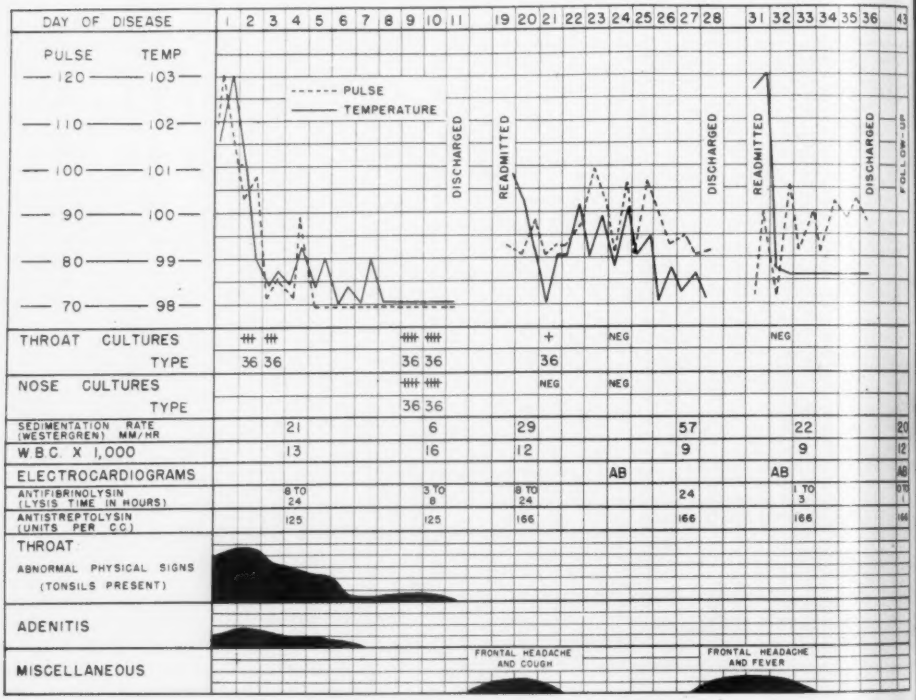

Chart 6.—Two episodes of poststreptococcic fever associated with carditis were observed in W. P., aged 24.

still abnormal. From the ninth to the twenty-sixth day he felt ill, ate poorly and lost 12 pounds (5.4 Kg.) in weight.

Because he had not regained his full strength and was fatigued easily on moderate activity, he was readmitted to the hospital on the fifty-fourth day for further study. During the following fifteen days he was essentially afebrile and felt fairly well, but the erythrocyte sedimentation rate became progressively more rapid, being 41 mm. per hour on the sixty-eighth day. Leukocyte counts and roentgenograms of the chest were normal. Serial electrocardiograms throughout the illness were normal.

His condition on discharge on the sixty-ninth day was unsatisfactory in that his strength was below normal and he felt ill. Further follow-up was not possible.

Comment.—Here is an example of a case in which a period of disability of more than two months was initiated by a monotype hemolytic streptococcic infection of the respiratory tract. During this entire period, easy fatigability and malaise were associated with a rapid erythrocyte sedimentation rate and, at times, low grade fever. There was no evidence of carditis.

Summary.—The convalescence of certain patients with hemolytic streptococcic sore throat was complicated by a recrudescence of fever.

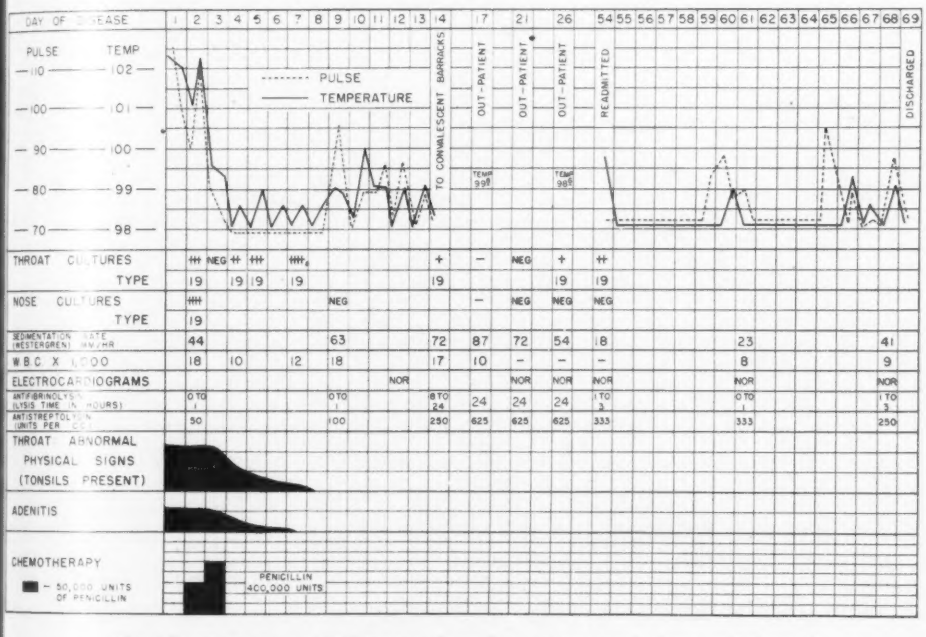

Chart 7.—J. G. O., aged 34, had prolonged poststreptococcic fever, malaise and a persistently elevated erythrocyte sedimentation rate.

The late febrile illness was associated with an elevated erythrocyte sedimentation rate, which frequently persisted for several weeks. Electrocardiographic but not clinical evidence of carditis was obtained in more than one third of this group.

These cases closely resemble those described previously in which rheumatic fever followed infection by hemolytic streptococci, except for the absence of arthritis. Important differences, however, were present. The late fever without involvement of the joints appeared earlier, was less severe, as estimated by the height of temperature and degree of abnormality of the electrocardiogram and erythrocyte sedimentation rate,

and was of shorter duration than in those cases in which arthritis was present. It should be emphasized that there was overlapping between the two groups in regard to the severity and duration of all these abnormalities.

CARDITIS

Electrocardiographic evidence of carditis was obtained for 11 patients convalescent from hemolytic streptococcic sore throat in whom arthritis and late fever were absent. The cases have been described elsewhere.[3e] Additional pertinent information is presented in table 3.

Electrocardiograms were available as early as the tenth day of the streptococcic illness in 6 cases and were already abnormal at that time

TABLE 3.—*Poststreptococcic Carditis: Clinical and Laboratory Data*

		Erythrocyte Sedimentation Rate*					Electrocardiogram			
Case No.	Infecting Type	First	Second	Third	Fourth	Day First Normal	Day First Done	Day First Abnormal	Duration of Abnormality, Days	Key No.†
34	30	77/2	56/15	30/21	84/28	Over 29	7	7	Over 21	8
35	36 and 6	27/1	39/9	35/14	31/24	Over 24	13	13	Over 38	19
36	17 and 1	75/3	48/14	20/21	35/34	Over 25	9	9	10	7
37	17 and 44	Not done	52/11	54/28	55/42	Over 42	28	28	Under 14	4
38	17 and 30	40/3	75/16	98/29	66/43	Over 50	11	29	7	15
39	46	96/3	90/15	27/42	23/41	Over 41	9	9	28	1
40	19	54/3	64/10	11/16	Not done	16	10	10	7	3
41	26	58/3	42/9	56/32	31/44	Over 44	13	32	Over 12	6
42	36	26/3	12/9	Not done	87/40	Over 40	9	40	Unknown	18
43	44	14/3	11/10	25/30	Not done	Over 30	13	13	Under 11	20
44‡	36 and 1	36/3	13/8	22/22	Not done	Over 22	8	8	Under 14	

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.

† Refers to number of the case under which electrocardiograms were described in a previous paper.[3e]

‡ T waves in lead II were of low voltage; in lead III they were inverted.

in 5. They remained so for more than seven days in 4 and more than twenty-one days in 2. Either the electrocardiogram became abnormal later, or earlier studies were not done on the other patients.

The erythrocyte sedimentation rate was invariably elevated at the time that evidence of carditis was first obtained, and it remained so for more than twenty days in 9 and more than forty days in 5 cases. All these men made a prompt recovery from the initial streptococcic infection and remained well. In none was clinical evidence of a continuing process elicited.

The electrocardiographic abnormalities were similar in nature to those present in patients with late fever or arthritis but were less decided and persistent than those noted in patients with involvement of the joints. Clinical signs of carditis were absent in all these patients.

Infection by a variety of serologic types of hemolytic streptococci preceded the development of carditis in this group. Bacteriologic evidence of reinfection by a new type was secured in 5 cases. In 3 this event was not associated with the development of the cardiac abnormality, but in 2 (cases 37 and 38) the relationship between the time of reinfection and the first appearance of an abnormal electrocardiogram was such as to indicate that the two occurrences were causally related.

Summary.—Abnormal electrocardiograms indicating the presence of carditis were discovered in men convalescent from hemolytic streptococcic sore throat who presented no clinical evidence of a continuing pathologic process. The erythrocyte sedimentation rate was elevated in all cases and usually remained so for three or more weeks.

LATE LYMPHADENITIS

Late lymphadenitis appearing during convalescence from hemolytic streptococcic sore throat has been regarded as a nonsuppurative complication of this disease. This concept was only partially correct as an explanation for the phenomenon in this group of patients. In certain cases it was difficult to be certain that a delayed extension of the suppurative process to the neighboring cervical glands had not occurred. In other patients, reinfection by a new type of hemolytic streptococcus during the convalescent period was associated with the development of tender adenitis in the anterior cervical region in the absence of pharyngeal signs which would have suggested that a new infection had occurred. This mechanism was positively identified as the cause in 7 examples of late adenitis, 5 as the result of reinfection during the food-borne epidemic in the hospital.[6] It was probably operative in cases 21 and 58 described in this paper.

There were 8 cases in which it was possible that nonsuppurative late lymphadenitis had supervened, since extensive bacteriologic investigation failed to reveal evidence of reinfection and the time of onset suggested that direct extension from the throat was improbable. The essential data are presented in table 4.

Adenitis was cervical in 7 cases and appeared from five to fifty days after the onset of the initial streptococcic infection. Glandular involvement was severe in 3 and moderately severe in the remaining cases. Abdominal pain began on the ninth poststreptococcic day in 1 man, and it continued for seven days. Physical examination of the abdomen revealed diffuse tenderness. It was believed that this episode was the result of abdominal lymphadenitis.

Fever accompanied the adenitis in 6 cases. The erythrocyte sedimentation rate was normal in 4 and only moderately elevated in 2 other patients during the period when lymphadenitis was extreme. In 3 other patients, a rapid erythrocyte sedimentation rate was observed at this

TABLE 4.—*Poststreptococcic Adenitis: Clinical and Laboratory Data*

Case No.	Infecting Type	Adenitis: Day of Onset	Adenitis: Duration, Days	Adenitis: Severity of Adenitis	Adenitis: Site of Adenitis	Late Fever: Day of Onset	Late Fever: Duration, Days	Late Fever: Maximum Temperature, F.	Erythrocyte Sedimentation Rate *: First	Second	Third	Fourth	Day First Normal	Serial Electrocardiograms
45	17	5	5	Severe	Cervical lymph glands	5	4	103.0	18/3	21/9	8/14	8/23	14	Normal
46	3	20	13	Moderately severe	Cervical lymph glands	Afebrile	Afebrile	98.6	14/2	6/8	3/13	2/33	2	Normal
47	17	50	5	Moderately severe	Cervical lymph glands	49	4	101.0	64/3	8/11	2/26	27/51	11	Not done
48	19	9	7	Severe	Abdominal lymph glands	10	6	101.0	Not done		42/18	Not done	Unknown	Not done
49	17	8	4	Moderately severe	Cervical lymph glands	5	5	100.0	10/3	15/10	3/19	Not done	3	Not done
50	Untypable and 26	Unknown		Moderately severe	Cervical lymph glands	Afebrile	Afebrile	98.6	39/3	35/8	40/19	43/28	40	Normal
51	Untypable	21	11	Extremely severe	Cervical lymph glands	23	9	102.0	22/3	13/11	6/24	3/36	8	Normal
52‡	Untypable and 46	..	..	.....	Cervical lymph glands									

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.

† Data on this case are given in the text.

time. Serial electrocardiograms were obtained for 5 of these patients and were always normal.

Infection by no particular serologic type of streptococcus was likely to lead to the development of late adenitis. Bacteriologic evidence of reinfection in 2 cases by an untypable strain was obtained, but the new organism was first isolated from the throat at such a time as to preclude its involvement in the process.

One case of late adenitis which presented many unusual features will be illustrated and described.

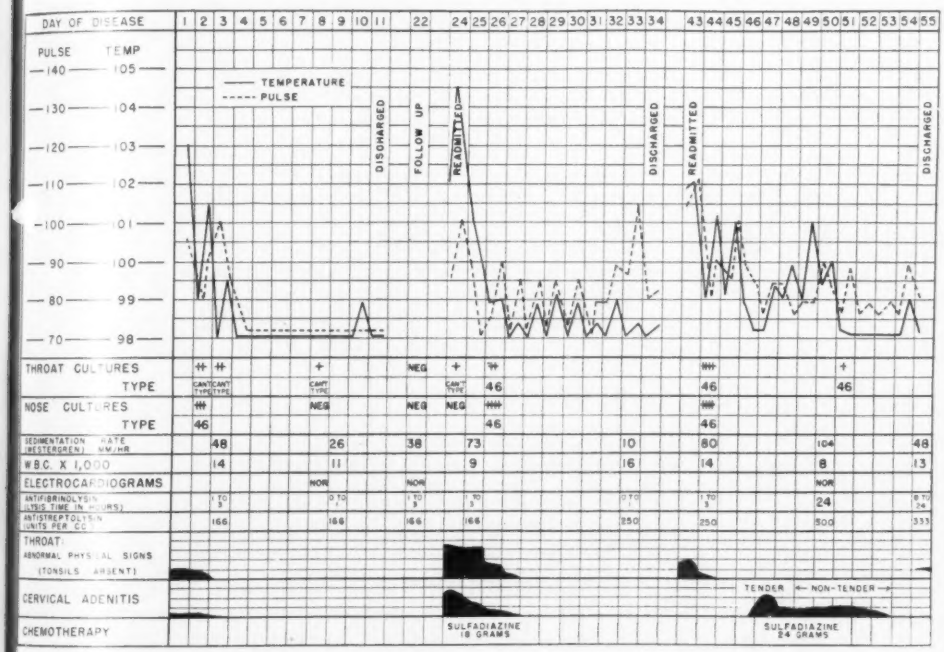

Chart 8.—Two episodes of poststreptococcic fever associated with cervical adenitis were seen in L. F. D., aged 24.

CASE 52 (chart 8).—A 24 year old man was admitted to the hospital on the first day of a moderately severe respiratory illness associated with few abnormal physical signs in the throat. Anteriorly, tender cervical adenitis was present but minimal. The erythrocyte sedimentation rate was elevated, and leukocytosis was discovered. Large numbers of untypable group A hemolytic streptococci were recovered from the pharynx and organisms of type 46 from the nose. The patient recovered promptly from this illness, but when he was seen in follow-up on the twenty-second day the erythrocyte sedimentation rate was still abnormal. No hemolytic streptococci were isolated from materials obtained from the nose or throat.

Two days later he reentered the hospital, suffering from another severe respiratory illness. On this occasion the throat was fiery red, exudate was present on the tonsillar tags and there were large tender glands in the anterior cervical region. Moderately severe gingivitis was also observed. Untypable hemolytic streptococci were present in the throat and organisms of type 46 in both nose and throat. The erythrocyte sedimentation rate was decidedly elevated. Sulfadiazine was administered, and he again recovered promptly.

Another febrile illness supervened on the forty-third day. On this occasion the throat was approximately normal, and there was no cervical adenitis until the fifth day in the hospital, when an extremely large and tender gland appeared on the right. The erythrocyte sedimentation rate, which had been 80 mm. per hour on the patient's admission, became more rapid and had not returned to normal by the time of his discharge. Large numbers of type 46 streptococci were present in the nose and throat. Recovery from the last illness occurred within ten days. Sulfadiazine was administered but was used too late to have been of value. A few electrocardiograms were obtained and were normal.

Comment.—The interpretation of the clinical course in this case is difficult. Three distinct febrile episodes were observed. Type 46 hemolytic streptococci were recovered from the upper air passages on all three and untypable organisms on the first two occasions. The most probable explanation of this sequence of events appears to require that the first illness be regarded as an initial hemolytic streptococcic sore throat and that the second be regarded as an instance of relapse, with recurrence of abnormal physical signs in the throat and adenitis. The last illness may be regarded as a nonsuppurative complication, with fever, extremely rapid erythrocyte sedimentation rate and late adenitis but with no local signs in the throat.

Summary.—Tender cervical and, probably, abdominal lymphadenitis may appear during convalescence from hemolytic streptococcic sore throat. This may be the result of delayed extension of suppuration from the pharynx or of reinfection by a new type of Streptococcus. In other cases it is probable that another, perhaps nonsuppurative, process is involved. Late lymphadenitis was somewhat different from other manifestations of the poststreptococcic state, as observed during this study, since it was frequently associated with a normal erythrocyte sedimentation rate and evidence of carditis was never discovered by electrocardiographic examination.

PNEUMONIA

In 3 men an illness associated with pneumonitis developed while they were convalescent from hemolytic streptococcic sore throat. Because the cases are of unusual interest all will be described and illustrated.

CASE 53 (chart 9).—A 23 year old man was admitted to the hospital on the second day of a moderately severe hemolytic streptococcic sore throat. Organisms of types 19 and 24 were isolated from the throat. He was clinically well within four days and was discharged on the ninth day, having received 10 Gm. of sodium salicylate daily. The erythrocyte sedimentation rate increased while he was hospitalized and after discharge. On the twenty-third day he returned to the outpatient clinic. At this time he felt ill and exhibited a little fever, the erythrocyte

sedimentation rate was 89 mm. per hour and the electrocardiogram was abnormal, the T waves being inverted in the standard leads (case 24 [36]). Higher temperature appeared on the next day, and he felt extremely ill.

The physical examination revealed nothing remarkable except for the presence of fine rales posteriorly over the lower part of the chest. A roentgenologic examination of the lungs four days later revealed the presence of a diffuse increase of the bronchial markings in the lower lobes of both lungs, similar to that often observed in primary atypical pneumonia. The leukocyte count was 15,000 per cubic centimeter, and the erythrocyte sedimentation rate was 107 mm. per hour on the fourth day in the hospital. An electrocardiogram at this time showed a

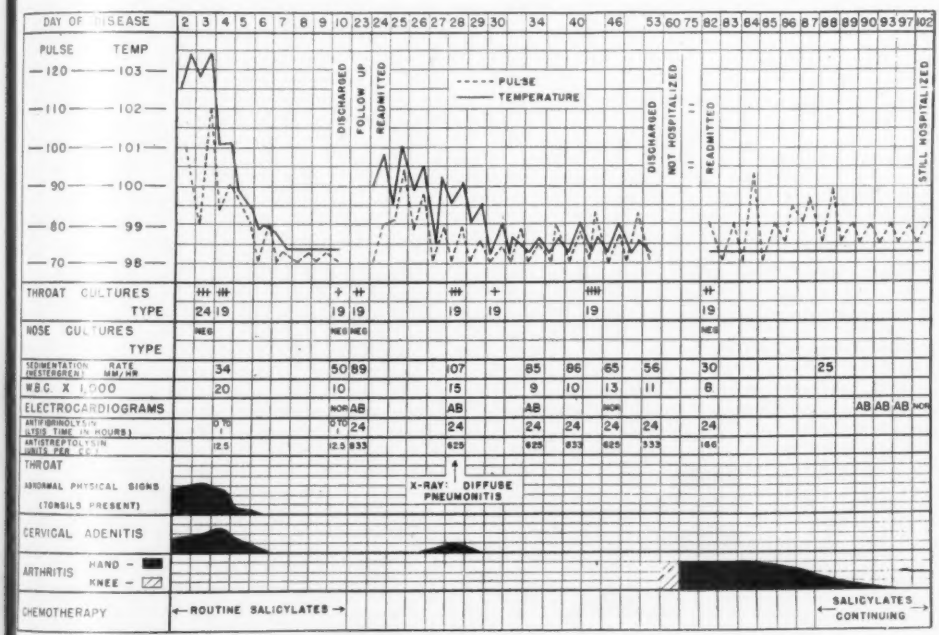

Chart 9.—J. D. E., aged 23, had poststreptococcic pneumonitis associated with carditis and followed by the development of arthritis.

prolongation of the P-R interval to 0.28 second. The T waves in all leads were isoelectric.

The patient's clinical recovery was complete in ten days, and the electrocardiogram returned to normal, but the erythrocyte sedimentation rate was 53 mm. per hour on the thirtieth day after the onset of the poststreptococcic fever. About three weeks later arthritis, associated with a rapid erythrocyte sedimentation rate but no fever, became manifest, and a prolongation of the P-R interval to 0.24 second was demonstrated. His symptoms subsided promptly after the administration of large amounts of sodium salicylate. Complete recovery had not occurred by the one hundred and third day, but no signs of valvular cardiac disease had appeared.

Comment.—This case demonstrates an example of fever and diffuse pneumonitis, associated with leukocytosis, a rapid erythrocyte sedimentation rate and abnormal electrocardiogram, following hemolytic streptococcic sore throat. A true latent period was absent. Later, typical mild rheumatic fever with carditis developed.

CASE 54 (chart 10).—A 21 year old man was admitted to the hospital on the second day of moderately severe sore throat caused by type 19 hemolytic streptococci, from which he recovered promptly without specific therapy. Pain in the left part of the chest and fever appeared on the fifth day. No abnormalities were discovered by physical or roentgenologic examination of the chest at that time. A pronounced leukocytosis was discovered on the eleventh day, which declined

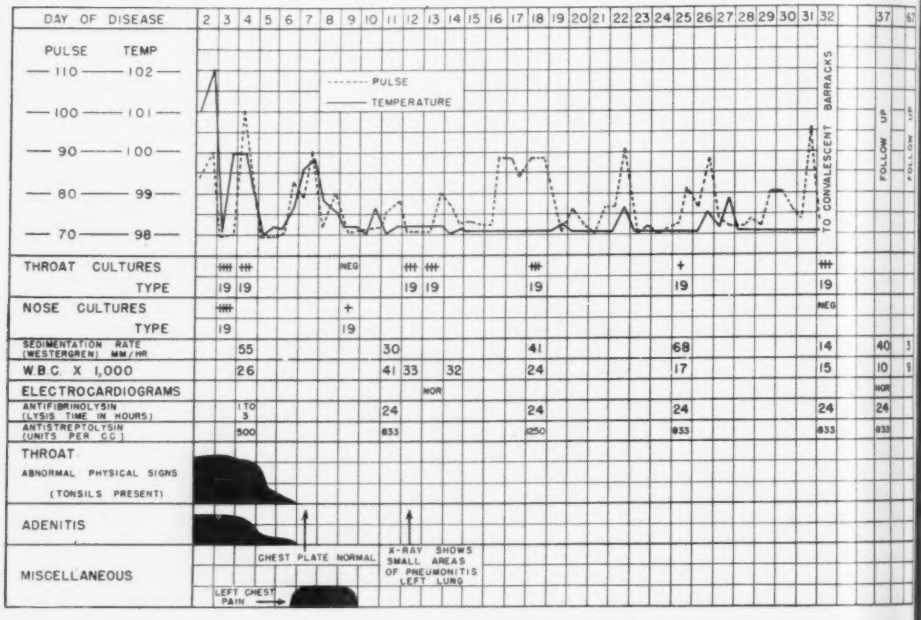

Chart 10.—R. E. C., aged 21, had poststreptococcic pneumonitis associated with an unusual degree of leukocytosis.

gradually but was still present on the thirty-second day. A roentgenologic examination of the chest on the twelfth day demonstrated patchy pneumonitis of the upper lobe of the left lung. He was essentially afebrile by the ninth day and remained so, but severe malaise persisted for more than four weeks and the erythrocyte sedimentation rate was still exceedingly rapid on the thirty-seventh day. Tachycardia was frequently observed during this period. Electrocardiographic study was inadequate.

Comment.—An example of pneumonitis associated with an unusual degree of leukocytosis and minimal fever following hemolytic streptococcic sore throat is here illustrated. Malaise persisted, and the erythrocyte sedimentation rate remained elevated for more than four weeks.

CASE 55 (chart 11).—A 19 year old youth was admitted to the hospital on the first day of an extremely severe sore throat caused by type 36 hemolytic streptococci, which was inadequately treated with penicillin. A clinical relapse followed the withdrawal of this agent. After this event he failed to become afebrile, felt ill and had pain in the chest, cough and severe headaches. The leukocyte count and erythrocyte sedimentation rates remained elevated. Repeated physical examination and roentgenologic studies of the chest failed to reveal abnormalities which would explain the prolonged disability.

The erythrocyte sedimentation rate had returned toward normal and he had clinically improved by the twenty-ninth day, and he was discharged a few days later, only to return on the thirty-sixth day. At that time fever and malaise were prominent, but the physical examination revealed nothing remarkable except for moderate redness and edema of the pharyngeal tissues. The erythrocyte sedimentation rate was abnormally rapid, but there was no leukocytosis. Hemolytic streptococci of two types, 36 and 17, were recovered from the nose and throat. Roentgenologic examination of the chest revealed patchy infiltration of the lower lobe of the left lung. He improved clinically and was afebrile on the fourth day in the hospital. Forty-eight hours later there was an abrupt rise in temperature, associated with the appearance of pain over the left part of the chest posteriorly. Physical examination of the lungs revealed no abnormalities, but roentgenologic study demonstrated diffuse pneumonitis involving most of the lower lobe of the left lung The character and distribution of the observed lesions were similar to those seen in cases of primary atypical pneumonia. The erythrocyte sedimentation rate became more rapid, and leukocytosis developed. Pneumococci and hemolytic streptococci were not recovered from the sputum.

The temperature returned to normal coincident with the administration of sulfadiazine, but the patient failed to make a complete recovery. Malaise persisted for several weeks, and the erythrocyte sedimentation rate was still abnormally rapid eighty-three days after the onset of the initial sore throat and forty-seven days after his second admission to the hospital.

Electrocardiograms were obtained on several occasions and were always normal.

Comment.—In this case, prolonged unexplained fever followed hemolytic streptococcic sore throat. Later, a type of Streptococcus different from that causing the initial illness appeared in the throat. This event was closely associated with the reappearance of fever and of pneumonitis, from which he recovered extremely slowly, the erythrocyte sedimentation rate being abnormally rapid more than six weeks later.

Summary.—Roentgenologic evidence of patchy pneumonitis was obtained for 3 men in whom poststreptococcic febrile illness developed. The involvement of the lungs was associated in every case with leukocytosis—in 1 case of an extreme degree—and a greatly elevated erythrocyte sedimentation rate. Electrocardiographic evidence of carditis was present in 1 case. Pneumococci were not present in the sputums of these patients, and hemolytic streptococci were recovered in only small numbers.

Recovery from the acute febrile disease occurred promptly, and the lungs cleared rapidly but the erythrocyte sedimentation rate remained abnormally rapid for more than four weeks in all cases. Arthritis developed approximately one month after the onset of pneumonia in 1 man

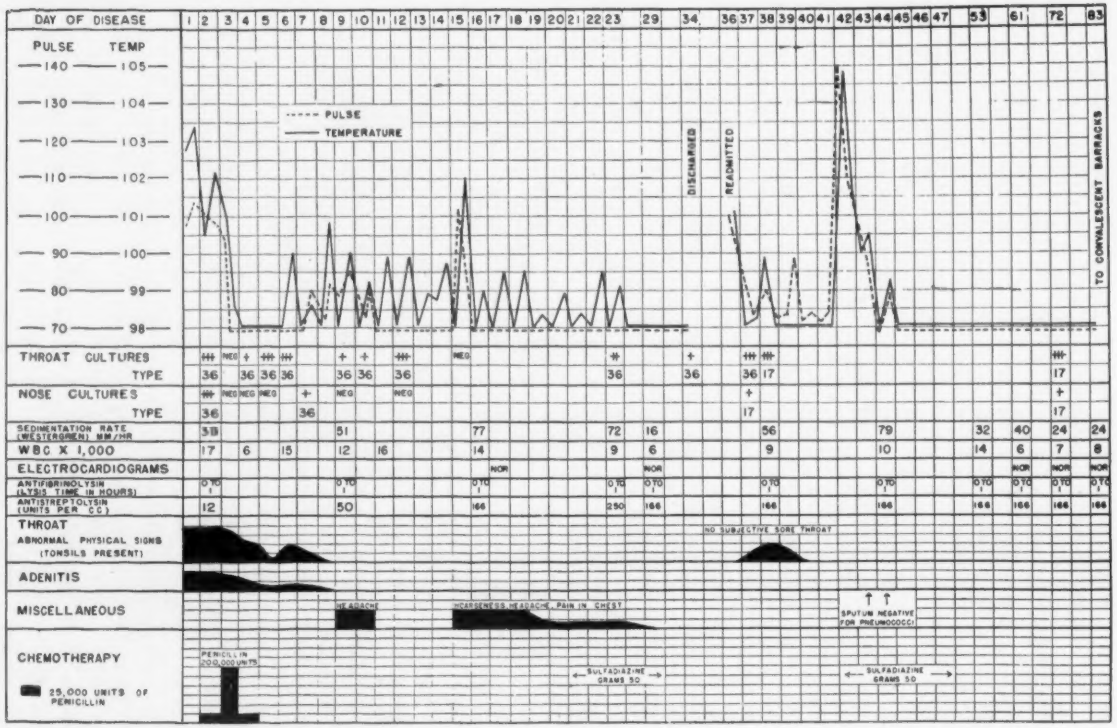

Chart 11.—Poststreptococcic pneumonitis following reinfection by a new serologic type of hemolytic streptococcus was observed in C. E. B., aged 19.

and was accompanied with a recrudescence of the electrocardiographic signs of carditis.

PERSISTENTLY RAPID ERYTHROCYTE SEDIMENTATION RATE

The erythrocyte sedimentation rate remained abnormally elevated for more than three weeks in 10 cases in which no evidence of a suppurative or nonsuppurative continuing disease could be discovered by clinical examination. The essential data are presented in table 5. In

TABLE 5.—*Persistent Poststreptococcic Prolongation of the Erythrocyte Sedimentation Rate: Clinical and Laboratory Observations*

Case No.	Infecting Type	Duration of Initial Fever	Erythrocyte Sedimentation Rate *					Serial Electrocardiograms
			First	Second	Third	Fourth	Day First Normal	
58	Described and illustrated							
59	Untypable and 17	2	61/3	32/9	37/22	Not done	Over 22	Normal
60	36	4	30/3	Not done	27/24	Not done	Over 24	Not done
61	36	2	34/2	Not done	65/26	Not done	39	Not done
62	17	6	9/3	25/9	21/15	25/24	Over 24	Not done
63	3	1	22/4	9/10	30/23	Not done	Over 23	Normal
64	3	2	21/3	9/10	Not done	28/49	Over 49	Normal
65	3	3	29/3	22/9	25/22	Not done	Over 22	Normal
66	1 and 12	2	55/3	31/9	46/18	46/28	40	Normal
67	Untypable	3	35/2	32/8	29/22	Not done	Over 22	Normal

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.

9 cases the erythrocyte sedimentation rate after three or four weeks was approximately as rapid as that observed initially or had increased. Serial electrocardiograms were obtained in 6 of these cases and were normal.

The course of the illness in 1 of these men is of particular interest and will be illustrated and described.

CASE 58 (chart 12).—An 18 year old youth was admitted to the hospital on the first day of a severe hemolytic streptococcic sore throat. Organisms of type 3 and of type 46 were isolated from the nose and throat. A prompt recovery was followed by an uneventful convalescence for a period of two weeks.

Severe tender adenitis of the anterior cervical region appeared on the seventeenth day, in association with a sharp rise in temperature and increase in the erythrocyte sedimentation rate and leukocyte count. The pharynx was approximateley normal on physical examination. This complication might have been regarded as nonsuppurative, but type 17 streptococci were now present in the throat, and it seemed clear that a reinfection had occurred.

Recovery from this disorder occurred quickly, and the patient returned to a state of full health. The erythrocyte sedimentation rate, however, remained extremely rapid for more than two months, having been 92 mm. per hour on the thirty-first day and 49 mm. per hour on the sixty-second day. Serial electrocardiograms were obtained between the tenth and thirty-ninth days and were normal.

Comment.—This case is an example of reinfection by a new type complicating convalescence from a hemolytic streptococcic sore throat and mimicking late nonsuppurative adenitis. The second infection was followed by a prompt return of a sense of well-being, but a continuing reaction of the tissue persisted for more than six weeks.

Summary.—The erythrocyte sedimentation rate remained abnormally rapid for three or more weeks in certain cases in which clinical evidence of a suppurative process as a cause for the prolonged reaction of the tissue was not obtained. Clinical and electrocardiographic signs indicating the presence of a continuing illness were absent.

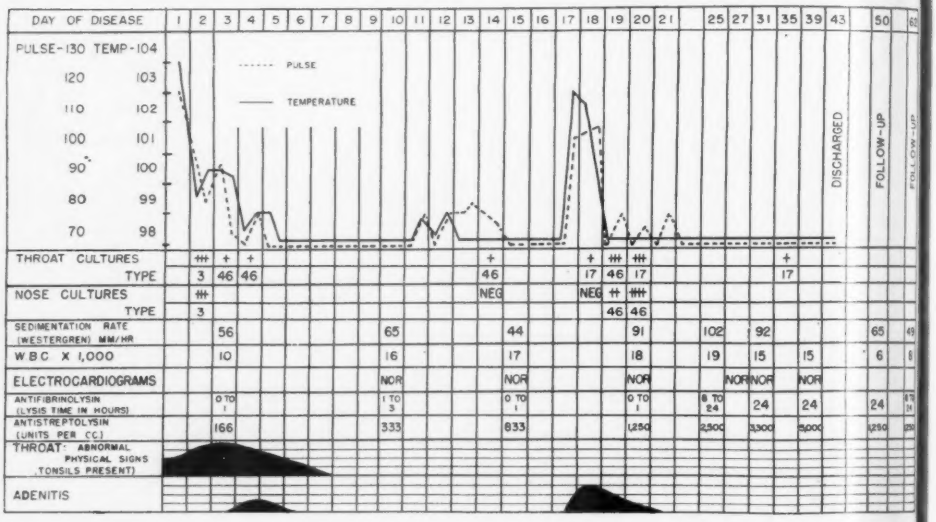

Chart 12.—Persistent elevation of the erythrocyte sedimentation rate following infection and reinfection by different types of hemolytic streptococci in A. S., aged 18.

PURPURA

Nonthrombopenic purpura followed hemolytic streptococcic sore throat in 2 cases, making its appearance in 1 on the ninth and in the other on the thirty-first day after the onset of the respiratory infection. The hemorrhagic areas were confined to the feet and legs in both cases. Sulfadiazine had been administered to 1 man during the four days preceding the onset of the purpura and in the other twenty-six days before. Prompt and uneventful recovery occurred in both cases.

It is impossible to determine whether the hemorrhagic disease in these cases was the result of the antecedent streptococcic sore throat, of the administration of sulfonamide drugs or of exposure to some unknown toxic agent.

GLOMERULONEPHRITIS

Clinically recognizable glomerulonephritis did not follow in any of the cases of hemolytic streptococcic sore throat during this study. Detailed serial examinations of urine, suitable for the detection of minor degrees of albuminuria or hematuria, were not performed.

PROLONGED INITIAL FEVER

A prolonged severe febrile illness of ten or more days' duration, which could not be explained on the basis of a suppurative complication, accompanied the initial phase in 5 cases of hemolytic streptococcic sore throat. The essential information in regard to these men is presented in table 6. The erythrocyte sedimentation rate was always extremely rapid during this febrile period, and electrocardiographic abnormalities were discovered in 4 cases. Evidence of carditis persisted for more than seven days in 4; and more than twenty days in 2 cases. It consisted in prolongation of conduction time in 3 cases, which was associated with changes in the T waves in 1, and the latter sign alone was present in 1 case.

The administration of sulfadiazine was followed by a termination of the febrile illness in only 1 of the 2 cases in which this drug was used. Two hundred thousand units of penicillin, administered in thirty-six hours, did not alter the course in another case. Salicylates were not given to any of these patients.

Two of these 5 men were followed for an insufficiently long period to define the natural history of the disease. The erythrocyte sedimentation rate, but not the electrocardiogram, had returned to normal by the twenty-first day in 1, the thirty-second day in another and the forty-seventh day in a third. The erythrocyte sedimentation rate remained rapid at the last examination of the other 2 patients on the twenty-eighth and thirty-sixth days of their illness. Abnormalities of the electrocardiogram also were demonstrable at that time in 1 in whom evidence of carditis had been previously discovered.

One of these cases of prolonged initial fever will be described and illustrated.

CASE 70 (chart 13).—A 34 year old man was admitted to the hospital on the first day of a severe sore throat caused by type 17 hemolytic streptococci. There were definite signs of maxillary sinusitis. No antibacterial therapy was instituted. He improved somewhat but remained febrile until the tenth day, when there was a sharp rise in temperature accompanied with a shaking chill. At that time, the physical examination revealed no definite abnormalities, and the signs of infection of the paranasal sinuses had disappeared. The culture of the blood was sterile.

Sulfadiazine was administered, and he rapidly became afebrile and remained so. He felt well by the twenty-eighth day, and the erythrocyte sedimentation rate

was declining. Electrocardiograms (case 13[86]) obtained at frequent intervals between the ninth and thirty-third days were always abnormal. The P-R interval increased from 0.20 second on the ninth day to 0.24 second on the nineteenth day and then decreased to 0.19 second on the thirty-third day. The T waves were always sharply inverted in leads I and II.

Comment.—This is an example of prolonged initial fever, complicating hemolytic streptococcic sore throat, which was not readily explained on the basis of

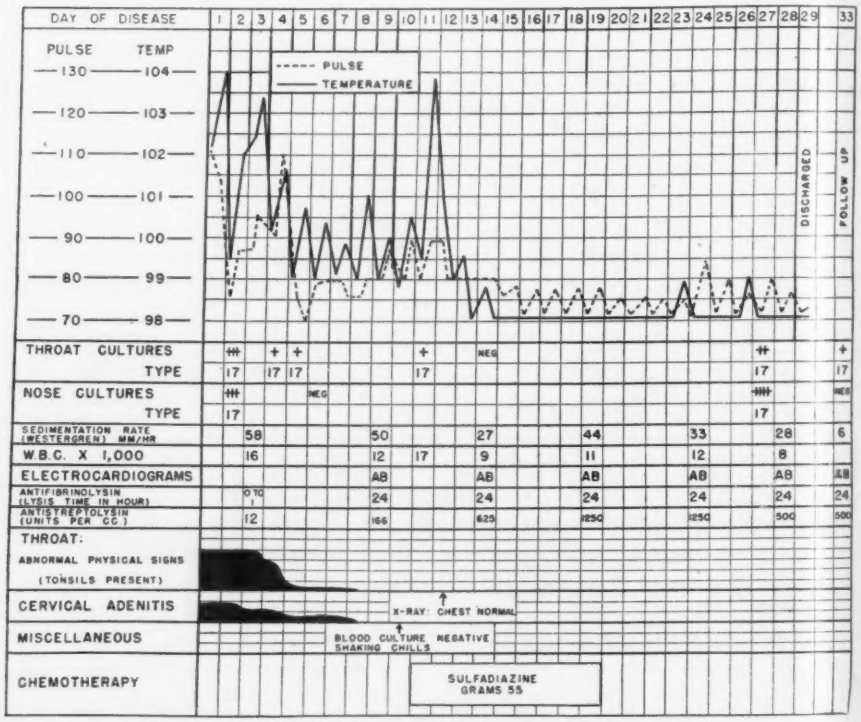

Chart 13.—Hemolytic streptococcic sore throat complicated by a prolonged initial fever and electrocardiographic evidence of carditis were seen in F. D. A., aged 34.

demonstrable continuing suppuration. Electrocardiographic evidence of carditis was present on the ninth day and persisted through the thirty-third day.

Summary.—Prolonged initial fever, not adequately explained on the basis of a diagnosable suppurative complication, was observed in 5 cases of hemolytic streptococcic sore throat. Electrocardiographic evidence of carditis was obtained for 4 of these cases. Complete recovery, with return of the erythrocyte sedimentation rate and electrocardiogram to normal, was delayed in certain cases.

TABLE 6.—*Prolonged Initial Streptococcic Fever: Clinical and Laboratory Data*

Case No.	Infecting Type	Initial Fever: Maximum Temperature, F.	Initial Fever: Duration, Days	Erythrocyte Sedimentation Rate *: First	Second	Third	Fourth	Day First Normal	Electrocardiogram: Day First Done	Day First Abnormal	Duration of Abnormality, Days	Key No.†
68	30	103.0	14	70/4	54/15	36/25	Not done	Over 25	10	Normal	Normal	0
69‡	46	103.0	11	37/2	49/8	33/14	7/47	Over 14	8	8	Over 7	
70	17	103.0	13	58/3	50/9	44/19	28/28	33	9	9	Over 28	13
71	17 and 36	103.0	10	23/3	75/11	5/32	Not done	Over 12	12	12	Over 20	2
72	46	103.0	10	53/3	38/12	21/16	5/21	21	14	14	Over 8	11

* Numerator is the erythrocyte sedimentation rate; denominator is the day following onset of streptococcic infection on which the test was done.

† Refers to the number of the case under which electrocardiograms were described in a previous paper.[3e]

‡ T waves of low voltage in leads I and II on first two examinations (on the eighth and fifteenth days). On the forty-seventh day the T waves were normal.

THERAPY

A number of therapeutic regimens were utilized in the treatment of the initial streptococcic sore throat in this group of patients. These have been described in detail elsewhere [3c] but may be summarized. Penicillin was administered intramuscularly in a short course (200,000 to 400,000 units in thirty-two hours), in a long course (500,000 to 1,000,000 units in eighty hours) and in a short course followed by sulfadiazine (an average of 39 Gm. in six and a half days). Ten grams of sodium salicylate per day was administered to another group from approximately the second to the tenth day of illness. Only symptomatic therapy was used in the management of 63.5 per cent of the patients.

Data pertinent to the evaluation of the effect of these several therapeutic regimens on the subsequent development of nonsuppurative complications after hemolytic streptococcic sore throat are presented in table 7.

TABLE 7.—*Effect of Therapy on the Development of Poststreptococcic Complications*

Therapy	No. of Cases	Arthritis		Late Fever		Carditis		Late Adenitis		Total of Arthritis, Late Fever, Carditis *	
		No.	%	No.	%	No.	%	No.	%	No.	%
Penicillin, short course	20	1	5.0	1	5.0	1	5.0	1	5.0	3	15.0
Penicillin, long course	13	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Penicillin and sulfadiazine	28	4	14.3	2	7.1	3	10.7	1	3.0	9	32.1
Sulfadiazine	37	1	2.7	1	2.7	1	2.7	0	0.0	3	8.1
Salicylates	27	0	0.0	2	7.4	1	3.7	0	0.0	3	11.1
None	217	13	6.0	8	3.7	5	2.3	6	2.8	26	12.0

* Three cases of poststreptococcic pneumonitis have not been included. One patient received a short course of penicillin and another sodium salicylate during the initial illness.

All the patients were not followed for identical periods or studied in comparable detail, and the number of cases in each chemotherapeutic category is small. Furthermore, chemotherapy was usually reserved for the most severely ill men. It was believed, however, that this information was of sufficient interest to deserve exhibition.

Particular emphasis is placed on the frequency of occurrence of arthritis, late fever and carditis, since these are almost certainly varying manifestations of a single pathologic process. The incidence of these three nonsuppurative complications was similar among untreated patients and those who received a short course of penicillin, sulfadiazine alone or sodium salicylate but was much higher in the group in which a short course of penicillin was followed by administration of sulfadiazine. No late complications of any kind occurred in patients who had received the long course of penicillin.

Summary.—The effect of antibacterial and salicylate chemotherapy of hemolytic streptococcic sore throat on the subsequent development of nonsuppurative complications has been analyzed. The treated and

untreated patients are not strictly comparable as to the nature and severity of the initial illness, and the number of cases in each category is too small to permit reliable analysis.

It is not believed that any conclusions whatever can be drawn from these data. They are presented for the information of other investigators. Nonsuppurative complications were absent in the group receiving 500,000 to 1,000,000 units of penicillin in eighty hours. It would, therefore, seem desirable to continue the study of the effect of the administration of this chemical to human beings infected by hemolytic streptococci to determine whether its use in such cases in large amounts will decrease the frequency of occurrence of the serious late nonsuppurative complications.

COMMENT

A large number of cases of sore throat caused by group A hemolytic streptococci in young adults was studied. Complete and uneventful recovery occurred frequently, but convalescence in many instances was marred by the development of a complication. Often this was the result of local suppuration, but in approximately 20 per cent of all cases a disorder supervened which could not be demonstrated to be the result of the local extension of the initial process in the throat or the invasion of remote tissues by hemolytic streptococci. A similar sequence of events has been observed by other investigators.[7]

Arthritis of varying degrees of severity was the commonest type of late nonsuppurative complication. Involvement of the joints was associated in certain cases with fever and clinical and/or electrocardiographic evidence indicating the presence of carditis. Such cases were then indistinguishable from cases of classic rheumatic fever. Fever or carditis often was absent. Demonstrable involvement of the heart was more likely to occur in febrile patients.

The febrile and arthritic phases of this poststreptococcic disorder were nearly always terminated by the administration of salicylates, but final recovery was delayed, the erythrocyte sedimentation rate having remained elevated in every case for more than thirty days.

The convalescence of another group of patients nearly as large as that just described was complicated by a recrudescence of fever, after a period of normal temperature following the initial respiratory illness, of from five to nineteen days in duration. Evidence of carditis in the form of abnormal electrocardiograms was discovered in more than one third of these cases. This febrile disease, except for the absence of involvement of the joints, closely resembled the arthritic poststreptococcic disorder just described, but there were important differences, as well

7. Watson, R. F.; Rothbard, S., and Swift, H. F.: The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, J. A. M. A. **128**:1145 (Aug. 18) 1945.

as similarities, between the two groups of cases. The complication appeared earlier, was less severe, as estimated by the degree of fever and the degree of abnormality of the erythrocyte sedimentation rate and electrocardiogram, and was of shorter duration if arthritis was absent.

Abnormalities of the electrocardiogram were discovered in another group of patients during convalescence from the initial streptococcic infection, in the absence of fever, arthritis or other clinical evidence of disease. The erythrocyte sedimentation rate was elevated in all these cases when evidence of carditis was first discovered, and usually it remained so for three or more weeks.

Involvement of the valves of the heart was not definitely recognized in any of the patients in the three categories just described during the relatively brief period of follow-up study that was available, nor was there clinical evidence of acute carditis in any except a few of the cases of arthritis. This may have been the result of the prolonged hospitalization of most of the patients during the period of intensive study. Others [8] have described cardiac pain, gallop rhythm, enlargement of the heart and collapse in similar patients subjected to more strenuous activity.

Three cases were studied that were of the greatest interest since a febrile disease associated with roentgenologic evidence of pneumonitis appeared during the poststreptococcic period. These cases would probably have been regarded as examples of primary atypical pneumonia if the initial streptococcic illness had not been observed and follow-up studies instituted. That this pneumonitis was a form of poststreptococcic nonsuppurative complication is strongly suggested by the following facts: 1. Pneumococci were absent from and hemolytic streptococci present in only small numbers in the sputum. 2. The clinical course of the disease was in no case that of ordinary hemolytic streptococcic suppurative pneumonia, since the disease was relatively mild and resolved promptly in all and without the use of chemotherapy in 2 cases. 3. The roentgenologic appearance of the lesion was not that usually presented by bacterial pneumonia. These observations indicate that pneumonitis in these men was not the result of direct invasion of the lung by hemolytic streptococci or by another organism. 4. The leukocytosis which was present in all would have been unusual in primary atypical pneumonia of probable virus origin, as would the exceedingly prolonged postpneumonic disability, with rapid erythrocyte sedimentation rate, which persisted for more than forty days in all cases.[9] 5. Definite abnormalities

8. Scherf, D.: Myocarditis Following Acute Tonsillitis, Bull. New York M. Coll. Flower & Fifth Ave. Hosp. **3**:252, 1940. Weinstein, J.: "Atypical" Coronary Disease in Young People, Ann. Int. Med. **21**:252, 1944.

9. Curnen, E. C.; Mirick, G. S.; Ziegler, J. E., Jr.; Thomas, L., and Horsfall, F. L., Jr.: Studies on Primary Atypical Pneumonia, Clinical Features and Results of Laboratory Investigations, J. Clin. Investigation **24**:209, 1945.

of the electrocardiogram, identical with those observed in other poststreptococcic disorders, were discovered in 1 man during the course of the pneumonic disease. Such evidence of carditis has not been observed in pneumonia of the virus type.[9] 6. Arthritis appeared in the patient just described while he was convalescent from pneumonitis.

Pneumonitis has long been recognized as a part of the syndrome of "rheumatic fever."[10] It is suggested that these examples of nonarthritic poststreptococcic pneumonia are examples of a related nonsuppurative process. Similar conditions have been observed by others following hemolytic streptococcic sore throat in military personnel.[11] Examination of the records of cases on which other reports were based, in which electrocardiographic abnormalities during the course of atypical pneumonia were described, strongly suggests that these were examples of poststreptococcic pneumonitis.[12]

In addition to these patients in whom clinical or electrocardiographic evidence of a disease process was discovered following hemolytic streptococcic sore throat, there were a few patients in whom the only sign of a continuing reaction of the tissue was a persistently elevated erythrocyte sedimentation rate in the absence of a demonstrable suppurative complication.

All these disorders, with or without arthritis or carditis, which have been observed to follow hemolytic streptococcic infection are believed to be manifestations of the same pathologic process. Their relationship to one another and their pathogenesis, so far as it may be elucidated by the present study and an analysis of previously reported investigations, have been fully considered elsewhere.[3d] It was suggested that these late complications of streptococcic disease were not the result of direct invasion of the affected tissues by the etiologic agent but of a more complex mechanism. An immunologic reaction, which occurred in persons whose tissues had been sensitized to some fraction or product of the hemolytic streptococcus as the result of previous infection by this organism, was a probable explanation for these phenomena.

The suggestion was made that all these disorders which are initiated by hemolytic streptococcic infections be grouped together and be regarded

10. Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, Medicine **7**:383, 1928. Jensen, C. R.: Nonsuppurative Poststreptococcic (Rheumatic Pneumonitis): Pathological Anatomy and Clinical Differentiation from Primary Atypical Pneumonia, Arch. Int. Med. **77**:237 (March) 1946.

11. Plummer, N.; Duerschner, D. R.; Warren, H. D.; Rogliano, F. T., and Sloan, R. H.: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, J. A. M. A. **127**:369 (Feb. 17) 1945.

12. (*a*) Finkelstein, D., and Klainer, M. J.: Pericarditis Associated with Primary Atypical Pneumonia, Am. Heart J. **28**:385, 1944. (*b*) Fuller, C. C., and Quinlan, J. W.: Acute Pneumonitis and Pericarditis: Report of a Case, New England J. Med. **229**:399, 1943.

as phases of the "poststreptococcic state." This concept states the essential streptococcic causation of rheumatic fever, adequately emphasizes nonarthritic poststreptococcic continuing disease as a potential cause of chronic valvular cardiac disease and simplifies the clinical consideration of the various manifestations of these conditions.

During the course of the investigation described here, certain other cases were observed in which complications followed streptococcic infection that were not clearly related to those enumerated here. Enlargement of the cervical lymph glands, with tenderness, developed in several men while convalescent from the initial infection. In certain cases this seemed to be caused by a delayed extension of the suppuration in the throat and in others was definitely the result of reinfection by a new type of hemolytic streptococcus. In the latter event, lymphadenitis appeared in the absence of the usual pharyngeal signs of streptococcic infection. There were a few patients in whom neither of these mechanisms could be established as the cause of late lymphadenitis and fever. The disease was, however, different from the other nonsuppurative complications described and may have another pathogenesis, because the erythrocyte sedimentation rate was usually normal during the height of the glandular involvement and later, and abnormalities of the electrocardiogram were never discovered.

Nonthrombocytopenic purpura, which may have been the result of the preceding streptococcic infection, occurred in 2 patients. A decision as to the cause of this complication cannot be made. Glomerulonephritis was not recognized as a sequel to hemolytic streptococcic infection during this study.

The initial sore throat was complicated by a prolonged febrile course, which could not be explained on the basis of any discovered continuing suppuration in 5 cases. Electrocardiographic abnormalities were present in 4 of these which were similar to those previously described in other cases included in this study. It may be that the prolonged disease in these cases was the result of hidden suppuration and that the alterations in the electrocardiogram were those which have been previously described in febrile persons.[13] It is not improbable that the early supervention of a nonsuppurative disorder similar to those described earlier had occurred, but this hypothesis cannot be definitely established.

Certain bacteriologic information obtained from study of the initiating streptococcic infection or infections has been included in the tables. The significance of these observations has been described and discussed elsewhere.[3d]

The treatment of the acute phase of hemolytic streptococcic sore throat by the administration of large amounts of sodium salicylate, a

13. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, Proc. Soc. Exper. Biol. & Med. **31**:931, 1934.

short course of penicillin alone or followed by a sulfonamide compound or the use of the latter drug alone did not prevent the development of late nonsuppurative complications. Poststreptococcic disorders were not observed in a small group of men who received 500,000 to 1,000,000 units of penicillin in eighty hours, but these results are not convincing, since the number of patients so treated was small.

Hemolytic streptococcic sore throat in young adults is a serious disease, the course of which may be complicated by the development of nonsuppurative disorders of which arthritis, fever and carditis in various combinations are the most important manifestations. Their recognition and proper management is of the greatest importance, since they prolong the period of disability, do not respond to the usual antibacterial chemotherapy and may be followed by the development of chronic valvular cardiac disease.

Intensive investigation of the phenomena of the poststreptococcic state is imperative for the purpose of discovering the pathogenesis of these disorders, technics for their recognition and methods for their prevention and treatment.

CARDIAC FAILURE IN PENICILLIN-TREATED SUBACUTE BACTERIAL ENDOCARDITIS

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SINCE the advent of penicillin in the treatment of subacute bacterial endocarditis, it has become increasingly obvious that certain patients are being cured of the infection only to suffer cardiac failure later. Many reports of treatment with penicillin mention cases in which there were unsatisfactory results, not because the drug failed to eliminate the bacteria but because of subsequent deterioration of cardiac function.[1] Inasmuch as the infection occurs in persons who have more or less damaged hearts to begin with and who might therefore be expected at some time to show symptoms of myocardial weakness, it seems illogical to blame penicillin unless its use can be shown to have hastened cardiac insufficiency. Obviously the drug cannot be expected to repair damage already done either by the original cardiac disease or by the bacterial endocarditis; the question is whether penicillin is likely to promote destructive processes. The purpose of this study is to determine (*a*) the part, if any, which administration of penicillin plays in promoting or postponing cardiac failure and (*b*) the factors in the patient with subacute bacterial endocarditis which predispose him to cardiac failure even if his vegetations are sterilized.

A. THE PART PLAYED BY PENICILLIN THERAPY IN CARDIAC FAILURE

1. *The Incidence of Cardiac Failure in Untreated Patients.*—To evaluate the significance of cardiac insufficiency in penicillin-treated patients, it is necessary to appreciate the incidence of cardiac failure

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1. (*a*) Loewe, L.: The Combined Use of Anti-Infectives and Anticoagulants in the Treatment of Subacute Bacterial Endocarditis, Bull. New York Acad. Med. **21**:59, 1945. (*b*) Meads, M.; Harris, H. W., and Finland, M.: Treatment of Bacterial Endocarditis with Penicillin: Experiences at Boston City Hospital During 1944, New England J. Med. **232**:463, 1945. (*c*) Bloomfield, A. L.; Armstrong, C. D., and Kirby, W. M. M.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. Clin. Investigation **24**:251, 1945. (*d*) Bloomfield, A. L., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **129**:1135 (Dec. 22) 1945. (*e*) Favour, C. B.; Janeway, C. A.; Gibson, J. G., and Levine, S. A.: Progress in the Treatment of Subacute Bacterial Endocarditis, New England J. Med. **234**:71, 1946.

in untreated patients. In order to emphasize the fact that symptoms of cardiac failure are not essential for the diagnosis of early subacute bacterial endocarditis, most observers have greatly underrated their incidence and have considered that cardiac insufficiency does not play an appreciable part in the course of the disease, even though often present terminally. The stress has been on the greater importance of embolic phenomena, sepsis or toxemia, and cardiac failure is considered but a result of exhaustion. Sir Thomas Horder observed that decompensation is so unusual in endocarditis that "we do not regard it as a disease of the heart at all." [2] Libman wrote that myocardial weakness occurred late and then was of "the type due to fever, anemia, and general weakness." [3] The myocardial insufficiency that Thayer observed in one fourth of his patients he considered to be merely one of the features of a "grave septicemia." [4] Sir Thomas Lewis found congestive failure one of the chief causes of death but considered that "it is always terminal." [5] White said that "rarely is there enough additional damage to the heart from this infection to cause heart failure directly." [6] Buchbinder and Saphir, however, found clinical cardiac failure of two to eight weeks' duration in 45 per cent of their patients and decided chronic passive congestion of the viscera at autopsy in 30 per cent more.[7] They described the uniform finding in their patients of extensive myocardial lesions adequate to explain cardiac failure apart from the effects of vague toxemia. They concluded that cardiac failure occurs in subacute bacterial endocarditis more frequently than is generally recognized and that it may be of some standing and not a mere terminal event.

My associates and I have reviewed 55 unselected cases of subacute nonhemolytic streptococcic endocarditis which were studied in this clinic in the ten years preceding the use of penicillin. Forty of the patients were examined at autopsy in the department of pathology, 13 having been followed in our clinic and 27 elsewhere. Seven other patients were followed in this clinic until death but were not examined at autopsy, and 8 were hospitalized here temporarily but were not adequately followed.

2. Horder, T.: The Clinical Significance and Course of Subacute Bacterial Endocarditis, Brit. M. J. **2**:301, 1920.

3. Libman, E.: The Clinical Features of Subacute Streptococcus Endocarditis, M. Clin. North America **2**:117, 1918.

4. Thayer, W. S.: Observations on Rheumatic Pancarditis and Infective Endocarditis, Ann. Int. Med. **5**:247, 1931.

5. Lewis, T.: Diseases of the Heart, New York, The Macmillan Company, 1937, p. 187.

6. White, P. D.: Heart Disease, New York, The Macmillan Company, 1944, p. 365.

7. Buchbinder, W. C., and Saphir, O.: Heart Failure in Subacute Bacterial Endocarditis, Arch. Int. Med. **64**:336 (Aug.) 1939.

The results in the cases which came to autopsy are recorded in table 1. A total of 10 patients (25 per cent) died of congestive failure. Twelve more (30 per cent) had symptoms and signs of cardiac weakness, such as dyspnea, orthopnea, rales at the bases of the lungs, engorgement of the liver and dependent edema, although the immediate cause of death was noncardiac, such as an embolic accident, renal failure or pneumonia. The duration of symptoms was from a few days to several months. In at least 1 case, symptoms of definite cardiac insufficiency antedated the infection by several years. Ten other patients (25 per cent) had no clinical symptoms or signs of myocardial weakness but on pathologic examination showed chronic passive hyperemia of the lungs and liver. Only 8 (20 per cent) had no clinical or pathologic evidence of cardiac failure. Therefore 80 per cent had evidence of some degree of myocardial insufficiency at the time of death. These

TABLE 1.—*Incidence of Cardiac Failure in Forty Untreated Patients with Subacute Bacterial Endocarditis*

	Cases Followed in This Clinic	Cases Followed Elsewhere, Autopsy Here	Total	Per Cent
Cardiac failure the cause of death	4	6	10	25
Cardiac failure present in some degree, but not the immediate cause of death	3	9	12	30
Pathologic but no clinical evidence of cardiac failure	3	7	10	25
No clinical or pathologic evidence of cardiac failure	3	5	8	20

figures correspond to those of Buchbinder and Saphir. Of the 7 patients followed until death but not examined pathologically, 2 died of cardiac failure, 2 had suggestive signs and 3 were not known to have signs of cardiac failure. Of the 8 who were seen but not followed, 1 had definite failure of fairly long standing, 2 had signs of early decompensation and 5 had no definite evidence of failure when last seen.

2. *The Incidence of Cardiac Failure in Penicillin-Treated Patients.*—In our series of 25 patients who have been followed for three to twenty-five months after completion of penicillin therapy, varying degrees of cardiac insufficiency have occurred in about 30 per cent. Of this group, 18 are alive and 7 are dead. As shown in table 2, 2 died of sudden accidents, thought to be cardiac, during therapy, 4 died of progressive cardiac failure after otherwise successful therapy and 1 died of an unrelated condition fifteen months later. Of the 18 who are alive, 3 have had definite signs or symptoms of cardiac failure and 15 have fairly good to excellent cardiac reserve. When the 2 who died of sudden accidents during treatment are included, cardiac failure developed in a total of 9 (36 per cent). When the 2 who died before the infection could be shown to have been eliminated are excluded, cardiac failure

has developed in 7 of 23 patients (30.4 per cent) in spite of eradication of the bacteria. Four of these patients (17.4 per cent) have died, and 3 (13 per cent) are living but require digitalis and rigid restriction of activity. Sixteen (69.6 per cent), therefore, have thus far escaped cardiac failure.

It may be concluded from these comparative studies that cardiac insufficiency is a potentially important complication in a large majority of untreated patients with subacute bacterial endocarditis and that as far as the group as a whole is concerned the use of penicillin postpones cardiac failure and reduces its incidence. Whether this is true in all individual cases is not settled by such statistics. As will be discussed

TABLE 2.—*Incidence of Cardiac Failure in Twenty-Five Patients with Subacute Bacterial Endocarditis Treated with Penicillin*

	Dead	Living	Per Cent of Whole Series	Per Cent of Those Cured of Infection
Sudden cardiac accident during treatment, before cure of infection	2	..	8	
Cardiac failure following otherwise successful treatment	4	3	28	30.4
No cardiac failure	1	15	64	69.6
Excellent cardiac reserve	..	7	28	30.4
Good cardiac reserve	1*	6	28	30.4
Fair cardiac reserve	..	2	8	8.7

* Died of an unrelated condition.

later, it seems in some instances that absorption of valvular vegetations under the influence of penicillin may, by further distorting the valve, actually hasten cardiac failure.[1d] In contrast to these few cases, however, are the many young persons with little previous cardiac damage who would certainly suffer some degree of cardiac failure in the course of their endocarditis, to say nothing of the other hazards, were it not for penicillin. The impression that use of penicillin promotes cardiac failure is probably due to the fact that it rescues patients from death due to embolic accidents or generalized sepsis long enough for them to suffer insufficiency of an already damaged myocardium. In general, therefore, the use of penicillin unmasks, rather than promotes, cardiac decompensation.

B. FACTORS WHICH DETERMINE CARDIAC RESERVE AFTER PENICILLIN TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

In order to aid preservation of good cardiac function after eradication of active bacterial endocarditis, it is desirable to have clearly in mind the reasons why some persons go through the infection unscathed while others become invalids with cardiac disease. In this study we

TABLE 3.—*Relationship of Various Factors to Cardiac Reserve After Penicillin Treatment in Twenty-Five Cases of Subacute Bacterial Endocarditis*

Name	Age, Yr.	Type of Lesion of the Heart	Cardiac Reserve Before Treatment	Appearance of Heart in the Roentgenogram	Time Until Adequate Treatment, Mo.	Average Daily Temperature, C.	Bacteria per Cc.	Clinical Appearance	Care After Treatment	Follow-Up Period, Mo.	Present Cardiac Reserve
1. L. C.	22	Congenital coarctation of aorta	Excellent	Large	3	38.8 (101.8 F.)	70	Good	Good	25	Excellent
2. E. G.	41	Mitral stenosis	Fair	Slightly large	3	39.0 (102.2 F.)	400	Poor	Good	3	Dead *
3. C. B.	34	Mitral stenosis	Fair	Slightly large	6	39.1 (102.3 F.)	Few	Poor	Poor	9	Dead *
4. M. T.	20	Aortic insufficiency	Excellent	Large	½	38.9 (102 F.)	25	Good	Good	24	Good
5. O. S.	58	Uncertain mitral disorder	Excellent	Normal	2	38.5 (101.3 F.)	25	Good	Good	23	Excellent
6. F. H.	59	Mitral stenosis	Fair	Slightly large	2	37.3 (99.1 F.)	40	Fair	Good	22	Poor
7. J. D.	64	Uncertain mitral disorder	Excellent	Normal	2	38.5 (101.3 F.)	25	Good	Good	22	Excellent
8. S. M.	18	Uncertain mitral disorder	Good	Slightly large	6	37.7 (99.8 F.)	8	Good	Good	21	Good
9. A. S.	64	Mitral stenosis	Good	Slightly large	2	38.5 (101.3 F.)	70	Good	Good	15	Good †
10. O. E.	29	Mitral stenosis	Poor	Large	1	39.3 (102.7 F.)	8	Poor	Good	12	Dead *
11. R. D.	23	Aortic insufficiency	Poor	Slightly large	3	39.8 (103.6 F.)	50	Poor	.....	..	Dead ‡
12. M. S.	22	Uncertain	Excellent	Normal	4	38.5 (101.3 F.)	100	Good	Good	18	Excellent
13. B. S.	23	Aortic insufficiency	Good	Large	5	38.9 (102 F.)	25	Fair	Good	17	Fair
14. V. T.	60	Aortic insufficiency; auricular fibrillation	Fair	Large	3	39.0 (102.2 F.)	80	Fair	.....	..	Dead ‡
15. R. L.	32	Aortic insufficiency	Good	Slightly large	2	38.0 (100.4 F.)	6	Good	Good	15	Good
16. M. P.	29	Aortic insufficiency	Excellent	Normal	3	38.0 (100.4 F.)	40	Good	Good	13	Excellent
17. V. D.	47	Aortic and mitral stenosis and insufficiency; auricular fibrillation	Poor	Large	1	38.1 (100.5 F.)	9	Fair	Good	13	Poor
18. M. D.	32	Aortic insufficiency	Good	Large	3	36.9 (98.4 F.)	3	Good	Good	11	Good
19. N. O.	47	Congenital septal defect	Excellent	Slightly large	7	38.7 (101.6 F.)	110	Good	Good	10	Excellent
20. J. H.	25	Aortic insufficiency	Good	Slightly large	½	37.8 (100 F.)	Few	Good	Good	10	Good
21. H. W.	27	Aortic insufficiency; paroxysmal auricular fibrillation	Excellent	Slightly large	1	38.5 (101.3 F.)	1	Good	Good	11	Good
22. E. J.	54	Aortic insufficiency	Good	Slightly large	2	38.4 (101.1 F.)	Few	Good	Poor	5	Poor
23. L. P.	69	Aortic insufficiency	Excellent	Slightly large	7	37.2 (98.9 F.)	Few	Good	Good	2	Dead *
24. F. S.	69	Aortic stenosis	Good	Slightly large	7	37.9 (102 F.)	40	Good	Good	3	Fair
25. J. K.	39	Uncertain mitral disorder	Excellent	Normal	14	38.1 (100.5 F.)	12	Good	Good	3	Excellent

* Died of progressive cardiac failure.
† Died of unrelated condition.
‡ Died of sudden cardiac accident during therapy.

have carefully compared our 25 patients to see what was the common denominator in the group whose hearts stood the infection well. It soon became obvious that there was no simple solution but that the sum total of a number of factors was responsible for the result.

The factors considered (table 3) were (1) the patient's age, (2) the type of antecedent lesion of the heart, (3) the cardiac reserve before treatment, (4) the size and shape of the heart, as shown by roentgenologic examination, (5) the length of time elapsing between onset of symptoms and start of adequate therapy, (6) the height of the temperature, (7) the intensity of bacteremia, (8) the general clinical appearance, (9) the extent of scarring of the valves as vegetations healed and (10) the care of the heart after therapy.

The factors which bear on cardiac reserve after penicillin therapy may be divided into (1) those operative before inception of treatment (the first eight) and (2) those to be considered afterward (the last

TABLE 4.—*Effect of Age on Cardiac Reserve After Therapy*

Age Group, Yr.	No Cardiac Failure		Definite Cardiac Failure			
			Alive		Dead	
	No.	%	No.	%	No.	%
Under 30	8	80	..	....	2	20
30 to 50	4	57.1	1	14.3	2	28.6
Over 50	4	50	2	25	2	25

two). Concerning the latter, it might be mentioned that there is no accurate measurement of the amount of scarring caused by absorption of valvular vegetations. It would seem, however, that the degree of distortion would be conditioned by the size and location of the vegetations, which in turn would depend on the situation before treatment was started.

1. *The Age of the Patient.*—A survey of the whole group suggests that youth favors a good result. Eighty per cent of those under 30 years escaped without definite cardiac failure, whereas only 50 per cent of those over 50 years were thus fortunate (table 4). Given 2 persons with apparently similar lesions of the valves, a young man seems to do better than an older man. On the other hand, the oldest patients as a whole had somewhat less extensive lesions of the valves than the youngest, probably because the patients with the worst cardiac conditions of their generation had already died.

2. *The Type of Lesion of the Heart* (table 5).—If the underlying cardiac disease is congenital there seems to be a better prognosis than if it is rheumatic, although the number of cases of congenital disease in this series is too small to be significant. Furthermore, if there are

indisputable signs of mitral stenosis or aortic insufficiency, the prognosis does not seem so good as when the type of cardiac disease or the nature of the lesion of the valve is uncertain. In this "uncertain" group, for instance, are those with lesions of questionable nature of the mitral valve, i. e., those with apical systolic murmurs but no definite diastolic murmur or other clearcut evidence of mitral stenosis. The presence of a serious arrhythmia (notably auricular fibrillation) seems to make the prog-

TABLE 5.—*Effect of the Type of Lesion of the Heart on Cardiac Reserve After Therapy*

Type of Lesion	No Cardiac Failure		Definite Cardiac Failure			
			Alive		Dead	
	No.	%	No.	%	No.	%
Congenital heart disease	2	100				
Uncertain type of lesion	5	100				
Definite aortic insufficiency or mitral stenosis	8	53.3	2	13.3	5	33.3
Definite lesion of valve and serious arrhythmia	1	33.3	1	33.3	1	33.3

nosis less favorable. It must be remembered that since these patients have previously damaged muscles and valves of the heart they might be expected eventually to show cardiac insufficiency independent of any effect of the bacterial endocarditis.

3. *Cardiac Reserve Before Therapy.*—There is, as would be expected, a high correlation between cardiac reserve before and after therapy (table 6). A few of the patients had long had cardiac symptoms and,

TABLE 6.—*Effect of Previous Cardiac Reserve on Cardiac Reserve After Therapy*

Previous Cardiac Reserve	No Cardiac Failure		Definite Cardiac Failure			
			Alive		Dead	
	No.	%	No.	%	No.	%
Excellent	9	90	..	....	1	10
Good	7	87.5	1	12.5		
Fair	..	....	1	25	3	75
Poor	..	....	1	33.3	2	66.6

of course, did not improve after treatment. Others insisted that they felt better since treatment than they did before because they had learned to take better care of themselves. Some had apparently good reserve before contracting the infection but were already on the verge of failure before administration of penicillin was begun.

In the evaluation of cardiac reserve a rating adapted for our purpose from that of the American Heart Association was used: (1) excellent (no symptoms of cardiac insufficiency on unrestricted activity); (2) good (no symptoms of cardiac insufficiency on slightly restricted activity); (3) fair (mild symptoms of cardiac insufficiency either on mod-

erate activity or under the stress of the infection), and (4) poor (frank symptoms or signs of cardiac failure either before the infection or under its stress).

Of the 18 patients who started out with excellent or good reserve, all but 2 are still in good health; of these, 1 is dead and 1 has definite cardiac failure. On the other hand, of the 7 patients who started treatment with fair or poor reserve, 5 are dead and 2 have definite cardiac failure.

4. *The Size and Shape of the Heart as Shown by Roentgenologic Examination.*—The use of the roentgenogram is another objective method of estimating cardiac reserve before therapy (table 7). Five patients had no cardiac enlargement, and all are now in good health. Thirteen had slight or questionable general cardiac enlargement or prominence of one part of the heart; of these, 6 are doing well, 2 have symptoms

TABLE 7.—*Relationship Between Size of Heart Before Treatment and Cardiac Reserve After Treatment*

Size of Heart as Shown in the Roentgenogram	No Cardiac Failure		Definite Cardiac Failure			
			Alive		Dead	
	No.	%	No.	%	No.	%
Normal	5	100				
Slightly large *	7	53.8	2	15.4	4	30.8
Large	4	57.1	1	14.3	2	28.6

* Includes those with slight prominence of one part of the shadow of the heart and with size "at the upper limits of normal."

of cardiac failure and 5 are dead (1 of an unrelated condition). Of the 7 who started out with considerable cardiac enlargement, 4 are doing well, 1 has chronic cardiac failure and 2 are dead. Except for the fact that all in the first group are doing well, there is then no absolute correlation. There is almost no difference between those with only slight abnormality of the cardiac silhouette and those with considerable enlargement. A number did badly who at first had only questionable cardiac hypertrophy, and several are doing well who started out with enlarged hearts. Incidentally, some of the youngest men had the largest hearts, and some of the oldest men had the smallest. This again suggests that the patients with the worst cardiac conditions die before they reach the older age groups.

5. *The Length of Time Between Onset of Symptoms and Beginning of Adequate Therapy.*—There is some correlation between the promptness of treatment and the results, but it is not so high as might be expected (table 8). Obviously, though, in the individual case the risk increases with time. Furthermore, several of the long periods include weeks or months of repressive therapy. Such subcurative therapy is

probably not entirely lost time. Several patients were finally treated successfully after long periods of inadequate but repressive therapy, varying from one month to about twelve months. Besides penicillin, sulfonamide drugs had also been given to some. On the other hand, there were 2 fatalities in cases in which the adequate dose was given only after time had been lost in subcurative treatment. In these cases, this period may have been critical.

TABLE 8.—*Effect on Cardiac Reserve of the Length of Time Between Onset of Symptoms and the Beginning of Adequate Therapy*

	No Cardiac Failure		Definite Cardiac Failure			
			Alive		Dead	
Length of Time, Mo.	No.	%	No.	%	No.	%
2 or less	7	63.6	3	27.3	1	9.1
2 to 4	4	57.2	..	....	3	42.8
Over 4	5	71.4	..	....	2	28.6

6. *The Height of the Temperature.*—There is obvious significant correlation between extremely high temperature and poor results, all the patients with an average temperature of 39 C. (102.2 F.) or over having died (table 9). However, with the other three groups the correlation is almost negligible. It might be concluded that unless the fever is unusually severe there is a good chance of getting a satisfactory result, other things being equal.

TABLE 9.—*Effect of the Height of Temperature on Cardiac Reserve After Treatment*

	No Cardiac Failure		Definite Cardiac Failure			
			Alive		Dead	
Average Daily Temperature	No.	%	No.	%	No.	%
Below 38 C. (100.4 F.)	4	66.6	1	16.7	1	16.7
38 to 38.4 C. (100.4 to 101.1 F.)	3	60	2	40		
38.5 to 38.9 C. (101.3 to 102 F.)	9	100				
39 C. (102.2 F.) or over	..	....	..	....	5	100

7. *The Intensity of Bacteremia.*—There would appear to be only little correlation between the number of bacteria and the results. The patient with the highest colony count (400 per cubic centimeter) did not survive, but otherwise there is no particular parallel. There is not even much relationship between the intensity of the bacteremia and the height of the temperature or the clinical appearance. The resistance of the organism to penicillin should be regarded as important mainly when it affects the length of time which elapses before the start of adequate treatment and therefore is not here considered as a factor influencing subsequent cardiac reserve.

8. *The General Clinical Appearance.*—Several patients looked so ill that they obviously constituted poor risks from the start. This appearance was in general a more accurate indication of the outcome than the measurable intensity of the bacteremia. Some patients looked well and apparently constituted good risks.

Taken together, the temperature, bacterial count and clinical appearance are measures of the severity of the infection and as such would be expected to strongly influence the results.

9. *Increased Distortion of the Valves Under the Influence of Penicillin.*—Several patients showed an apparent acceleration of the destructive process while they were getting penicillin. Admitting that it is hard to separate the results of the disease from those of treatment, it seemed in some cases that the sudden failure of the heart was out of proportion to the conditions present at the start of treatment. L. P. is the leading example. Except for the facts that he was an older man with a definite aortic insufficiency and had had a period of subcurative therapy, there was much in his favor. He felt well, had almost no fever, had few bacteria and had no signs of failure. Nevertheless, just when the lesions should have been healing well there developed sudden alarming cardiac insufficiency, from which he never recovered. It seemed not unlikely that as the vegetations healed his valve was increasingly scarred and distorted.

E. J. had long been followed in the clinic with the diagnosis of aortic stenosis, never having shown the physical signs of aortic insufficiency despite numerous attempts to discover them. However, a few weeks after treatment was started there appeared a faint aortic diastolic blow which subsequently became loud. It is hard to say how much of this structural change was due to the infection and how much to the resolution of the lesion under the influence of penicillin, but it seems that the latter must be considered until more evidence is forthcoming.

10. *Care of the Heart After Treatment.*—Another important factor after therapy is reasonable restriction of activity. This is, of course, an individual matter, inasmuch as what would be reasonable activity in one might be excessive in another. However, this problem is not peculiar to patients cured of subacute bacterial endocarditis; it is a fundamental problem of cardiology in general. At least 2 of our patients, under social and economic pressure, greatly transgressed the limits of reason in this respect despite repeated warnings, and both suffered cardiac failure as a result. On the other hand, most of the patients have taken their infection as a warning and have learned to live within reasonable restrictions, so that they profess to feel better now than before they were stricken with the disease. Only years of observation will tell whether or not their life expectancy will be significantly reduced.

COMMENT

The important factors which seem to determine cardiac efficiency after therapy are the reserve and size of the heart at the time treatment is begun, the patient's age, the type of lesion of the heart, the general clinical appearance and the height of the temperature. In the individual case, some of these factors become more and more unfavorable as adequate treatment is postponed, although, statistically, the time between onset of disease and start of treatment bears less correlation.

As important as these factors are, no one of them can be correlated exactly with the outcome. For instance, L. P. had an extremely low temperature and M. T. a fairly high one; yet there was a good result in the latter and a poor result in the former. Likewise, C. D. had

TABLE 10.—*Values Used in Rating the Liability of Patients to Cardiac Failure After Treatment with Penicillin*

1. Age:		5. Length of time until treatment:	
Below 30	1	Under 2 months	1
30 to 50	2	2 to 4 months	2
Above 50	3	Over 4 months	3
2. Type of lesion of the heart:		6. Height of average temperature:	
Congenital	1	Under 38 C. (100.4 F.)	1
Uncertain	2	38 to 38.4 C. (100.4 to 101.1 F.)	2
Definite mitral stenosis or aortic insufficiency	3	38.5 to 38.9 C. (101.3 to 102 F.)	3
Serious arrhythmia	4	Over 39 C. (102.2 F.)	4
3. Previous cardiac reserve:		7. Bacteria per cc.:	
Excellent	1	Less than 50	1
Good	2	More than 50	2
Fair	3	8. General clinical appearance:	
Poor	4	Good	1
4. Roentgenologic appearance of the heart:		Fair	2
Normal	1	Poor	3
Slight enlargement	2	9. Care of the heart after treatment:	
Considerable enlargement	3	Good	0
		Poor	2

fever for only one month, and J. K. had fever for fourteen months; yet the former is dead, and the latter is in good health. R. D., a young man, died before treatment was complete, whereas J. D., an old man, does hard physical work without the slightest difficulty two years after therapy. C. B. was an athlete, whereas V. D. had mild cardiac failure and auricular fibrillation for years; yet the former is dead, and the latter manages to get along not much worse than he did before treatment.

It seems, therefore, that the outcome is a composite result of several factors. Although the more one feature is against a patient, the less are his chances, yet if other things are favorable he may survive without appreciable deterioration of cardiac function. It is a combination of unfortunate circumstances, not just one, which makes extirpation of the infection a Pyrrhic victory.

A fairly accurate prognosis can be made by estimation of the combined effect of various factors. For instance, if numerical values are assigned to each of the various factors (table 10), the sum total, or

"liability rating" of a patient, approximates fairly closely the actual status after treatment (table 11). All our patients with a total "liability rating" of more than 19 are dead, whereas all with a rating of less than 16 are alive and in good health (with the exception of L. P.). In the case of L. P. and the intermediate group, it may well have been the unmeasurable increase of valvular distortion under the influence of penicillin which was critical.

Of all the factors discussed, the only one which is really amenable to change by the physician is the length of time between onset of symptoms and the start of adequate therapy. However, several of the most alarming features—high temperature, general clinical appearance and, most important of all, the cardiac reserve at the beginning of therapy—are more or less functions of the length of time consumed while the patient awaits the start of therapy. For instance, when penicillin first

TABLE 11.—*Liability Rating Compared with Present Cardiac Reserve*

Name	Rating	Present Status	Name	Rating	Present Status
C. B.	23	Dead	M. D.	15	Good
V. T.	23	Dead	L. C.	14	Good
E. G.	21	Dead	M. T.	14	Good
C. D.	20	Dead	R. L.	14	Good
R. D.	20	Dead	H. W.	14	Good
V. D.	19	Poor	O. S.	13	Excellent
A. S.	18	Dead	J. D.	13	Excellent
B. S.	18	Fair	S. M.	13	Good
E. J.	17	Poor	J. K.	13	Excellent
F. H.	16	Poor	M. S.	12	Excellent
L. P.	15	Dead	M. P.	12	Excellent
F. S.	15	Fair	J. H.	12	Good
N. C.	15	Good			

became available for treatment of subacute bacterial endocarditis, we used it in several patients, in whom the disease was obviously well advanced. One of these (C. B.) had been an athlete before the onset of infection but had signs of early cardiac failure by the time treatment was started. There is every reason to believe that he would not have suffered subsequent fatal decompensation had we been able to treat him a few months earlier. It is of interest that none of the patients we have treated recently have been nearly so ill. In general they have been treated before the process had gone to this apparently irreversible stage, and the incidence of cardiac failure has seemed to decrease.

If this wasted time is to be reduced to a minimum, two imperative demands confront the physician: (1) early diagnosis of the nature of the disease and (2) determination of the organism's degree of resistance to penicillin. Both are obviously necessary; the first is in itself not enough. Failures will continue to occur if subacute bacterial endocarditis is unsuspected or if precious time is lost in giving subcurative doses of penicillin.

SUMMARY AND CONCLUSIONS

1. Cardiac failure is important, or potentially so, in a large majority of untreated patients with subacute bacterial endocarditis. Eighty per cent of our series of 40 untreated patients followed to autopsy had evidence of cardiac failure of more or less chronicity.

2. Statistically, treatment with penicillin postpones cardiac failure and reduces its incidence. Approximately 30 per cent of our series of 25 treated patients suffered cardiac failure.

3. Cardiac failure after otherwise successful treatment is the result of an interplay of a number of factors, no one of which is exclusively responsible.

4. The most important factors are the previous reserve and size of the heart, the patient's age, the type of lesion of the heart, the height of the temperature, the general clinical appearance and the length of time before adequate treatment.

5. The one factor amenable to change by the physician is the length of time elapsing before the start of adequate therapy. This demands (*a*) early diagnosis of the nature of the disease and (*b*) determination of the degree of the organism's resistance to penicillin.

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MERCURIAL DIURETICS

A Comparison of Acute Cardiac Toxicity in Animals and the Effect of Ascorbic Acid on Detoxification in Their Intravenous Administration

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ACUTE toxicity of mercurial diuretics has been noted frequently, but no extensive investigation of substances to counteract this toxicity has been reported.[1] There are two apparently distinct immediate reactions in human beings—a nonfatal hypersensitivity [2] and a fatal cardiac reaction. Experiments in animals [1a] and observations in human beings [1c] have determined that death is caused by ventricular fibrillation.

Ascorbic acid has been used to detoxify chemotherapeutic heavy metals, especially arsenic.[3] It is an effective physiologic reducing agent. Certain animals, including dogs, can synthesize ascorbic acid and are therefore suitable experimental animals.

We have extended the investigation of the mechanism of immediate death in dogs from mercurial diuretics for the three commonly employed ones, mercurophylline injection, mersalyl and theophylline and mercuhydrin. We have also studied the possible detoxifying effect of ascorbic acid on these preparations.

The addition of another substance to a mercurial diuretic in an effort to prevent fatal reactions should have, according to Pines and his asso-

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Read before the Central Society for Clinical Research, Chicago, Nov. 1, 1946.

This research was aided in part by a grant from the M. D. Anderson Foundation.

From the Department of Medicine, Baylor University College of Medicine, and Hermann Hospital.

1. (*a*) Barker, H. M.; Lindberg, H. A., and Thomas, M. E.: Sudden Death and Mercurial Diuretics, J. A. M. A. **119**:1001 (July 25) 1942. (*b*) DeGraff, A. C., and Nadler, J. E.: A Review of the Toxic Manifestations of Mercurial Diuretics in Man, ibid. **119**:1006 (July 25) 1942. (*c*) Volini, I. E.; Levitt, R. O., and Martin, R.: Sudden Death Following Mercurial Diuresis, ibid. **128**:12 (May 5) 1945. (*d*) Wexler, J., and Ellis, L. B.: Toxic Reactions to the Intravenous Injection of Mercurial Diuretics, Am. Heart J. **27**:86 (Jan.) 1944.

2. Wolf, I. J.. and Bongiorno. H. D.: Sudden Death with Salyrgan, Canad M. A. J. **25**:73 (July) 1931.

3. Bundesen, H. N.; Aron, H. C. S.; Greenbaum, R. S.; Farmer, C. J., and Abt, A. F.: The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy, J. A. M. A. **117**:1692 (Nov. 15) 1941.

ciates,[4] three qualities. It should not decrease the diuretic effect, but, on the other hand, it should increase it. It should be innocuous in the dose recommended and should be miscible without forming a precipitate.

Ascorbic acid in combination with mercurophylline injection has been found by one of us (C. F. S.)[5] to increase the diuretic effect in human beings up to 50 per cent. This substance can be given intravenously in large doses without producing a toxic reaction. It can be mixed with mercurial preparations prior to administration without forming a precipitate.

METHOD

Mercurophylline injection (Campbell Products, Inc.), mersalyl and theophylline (Winthrop Chemical Company, Inc.) and mercuhydrin (Lakeside Laboratories, Inc.) were administered alone and in conjunction with ascorbic acid (Abbott Laboratories). The ascorbic acid was injected before and with the aforementioned preparations at different intervals of time. The dogs used in these experiments were maintained in anesthesia with a 2.5 per cent solution of pentobarbital sodium and were connected with an artificial respirator.

In the control dogs, mercurophylline injection, mersalyl and theophylline and mercuhydrin were administered in doses of 1 cc. into the femoral vein at two and five minute intervals. Ascorbic acid was administered in doses of 150 mg. ten minutes prior to the injection of 1 cc. of mercuhydrin at two minute intervals, and 250 mg. was mixed with 1 cc. of each of the mercurial preparations and given simultaneously at two and five minute intervals. Electrocardiographic records were obtained before and during the injection. Lead II was used to demonstrate the conduction disturbances. The lethal dose of a mercurial preparation was considered to be the development of bradycardia of less than 30 beats per minute or a ventricular asystole or a ventricular fibrillation.

RESULTS

A comparison of the lethal doses for mercurophylline injection, mersalyl and theophylline and mercuhydrin is shown in table 1. It can be noted that mercuhydrin was the least toxic of the three mercurial preparations employed, whereas mercurophylline injection and mersalyl and theophylline were about equal in toxicity.

It is to be noted in table 2 that the lethal doses of mercurophylline injection and of mersalyl and theophylline were not altered by the administration of ascorbic acid. The lethal dose of mercuhydrin, on the other hand, was definitely increased when ascorbic acid was administered either prior to or simultaneously with mercuhydrin.

The mechanism of the death from cardiac toxicity produced by mercurophylline injection and by mersalyl and theophylline either alone

4. Pines, I.; Sanabria, A., and Hernandez Arriens, R. T.: Mercurial Diuretics: The Addition of Magnesium Sulfate to Prevent the Toxic Effects of Their Intravenous Administration, Brit. Heart J. **6**:197 (Oct.) 1944.

5. Shaffer, C. F.: The Diuretic Effect of Ascorbic Acid: Preliminary Report on Its Use in Cardiac Decompensation, J. A. M. A. **124**:700 (March 11) 1944.

or with ascorbic acid is due to ventricular fibrillation, as noted in figures 1 and 2. Death following administration of mercuhydrin alone or in combination with ascorbic acid is due to ventricular asystole, as noted in figure 3.

COMMENT

Fatalities in human beings occur suddenly after the administration of a mercurial diuretic. Death has been attributed to ventricular fibril-

TABLE 1.—*The Lethal Doses for Mercurophylline Injection, Mersalyl and Theophylline and Mercuhydrin Administered Intravenously to Dogs*

Drug	No. of Dogs	Average Weight, Kg.	Amount Given at 2 and 5 Min. Intervals, Cc.	Average Total Given at 2 Min. Intervals (6 Dogs), Cc.	Average Total Given at 5 Min. Intervals (5 Dogs), Cc.	Minimum Lethal Dose/Kg. at 2 Min. Intervals, Cc.	Minimum Lethal Dose/Kg. at 5 Min. Intervals, Cc.
Mercurophylline injection.....	11	6.1	1.0	2.0	1.2	0.29	0.14
Mersalyl and theophylline...	11	6.4	1.0	2.2	3.0	0.52	0.52
Mercuhydrin.....	11	7.3	1.0	8.3	11.0	1.14	1.52

TABLE 2.—*The Lethal Doses for Mercurophylline Injection, Mersalyl and Theophylline and Mercuhydrin Combined with Ascorbic Acid and Administered Intravenously to Dogs*

Drug	No. of Dogs	Average Weight, Kg.	Amount of Mercurials Given at 2 and 5 Min. Intervals, Cc.	Amount of Ascorbic Acid Given/Cc. of Mercurials, Mg.	Amount of Ascorbic Acid Given Prior to Mercuhydrin, Mg.	Average Total Given at 2 Min. Intervals, Cc.	Average Total Given at 5 Min. Intervals (5 Dogs), Cc.	Minimum Lethal Dose/Kg. at 2 Min. Intervals, Cc.	Minimum Lethal Dose/Kg. at 5 Min. Intervals, Cc.
Mercurophylline injection.....	10	5.2	1.0	250	...	1.0 (5 dogs)	1.4	0.18	0.31
Mersalyl and theophylline...	10	7.6	1.0	250	...	3.2 (5 dogs)	3.0	0.41	0.40
Mercuhydrin.....	17	6.8	1.0	250	150	11.4 (7 dogs)	16.8	1.74	2.47
						12.8 (5 dogs)*		1.69*	

* Given ascorbic acid ten minutes prior to mercuhydrin.

lation.[1c] Any substance, therefore, that prevents death following administration of a mercurial diuretic should have an immediate detoxifying effect. Ascorbic acid, according to our studies, reduces the toxicity of mercuhydrin.

The mechanism of death from cardiac toxicity produced by mercurials in animals has been demonstrated to be relatively constant and independent of anesthesia, sectioning of nerves and perfusion of an isolated heart.[1a]

DeGraff and Lehman,[6] in a report on the acute toxicity of the mercurial diuretics, stated that the lethal dose of a mercurial diuretic in animals is inversely proportional to the rate of injection. This has been explained by Modell,[7] in that certain substances develop their actions slowly, and consequently, when injected rapidly, the true minimal lethal dose may be exceeded.

The average mean lethal dose for mercuhydrin when given at two minute intervals was definitely less than that with five minute intervals. The average mean lethal dose for mercurophylline injection or mersalyl

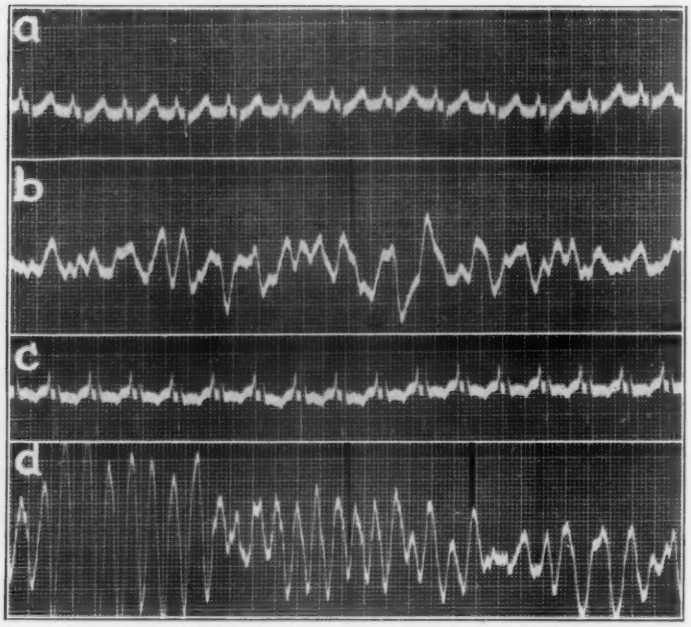

Fig. 1.—(*a*), lead II of a control prior to intravenous administration of mercurophylline injection. (*b*), ventricular fibrillation after injection of 1 cc. (*c*), lead II of a control prior to intravenous injection of mercurophylline and ascorbic acid. (*d*), ventricular tachycardia proceeding to ventricular fibrillation after injection of 2.25 cc. (1 cc. of mercurophylline injection and 1.25 cc. of ascorbic acid).

and theophylline when given at five minute intervals was not significantly different, however, from that at two minute intervals. This may be explainable on the basis of the mechanism of cardiac failure produced

6. DeGraff, A. C., and Lehman, R. A.: The Acute Toxicity of Mercurial Diuretics, J. A. M. A. **119**:998 (July 25) 1942.

7. Modell, W., and Krop, S.: Acute Toxicity of Mercurial Diuretics, Proc. Soc. Exper. Biol. & Med. **55**:80 (Jan.) 1944.

by mercuhydrin as compared with that produced by the other two mercurial preparations.

All the dogs receiving mercurophylline injection alone or in combination with ascorbic acid died in ventricular fibrillation. All but 1 of the dogs given mersalyl and theophylline either alone or with ascorbic acid also died in ventricular fibrillation. The 1 animal in which ventricular asystole developed tolerated more than twice the amount of this preparation than the average of the others receiving mersalyl and

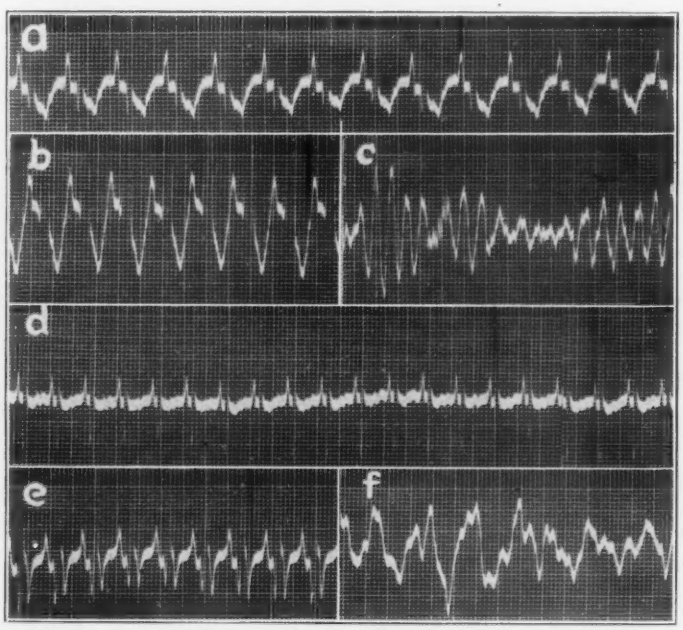

Fig. 2.—(*a*), lead II of a control prior to intravenous administration of mersalyl and theophylline. (*b*), ventricular tachycardia after injection of 1 cc. (*c*), ventricular fibrillation after injection of 2 cc. (*d*), lead II of a control prior to intravenous administration of mersalyl and theophylline and ascorbic acid. (*e*), altered ventricular complexes after injection of 4.5 cc. (2 cc. of mersalyl and theophylline and 2.5 cc. of ascorbic acid). (*f*), ventricular fibrillation after injection of 6.75 cc. (3 cc. of mersalyl and theophylline and 3.75 cc. of ascorbic acid).

theophylline. In contrast, all but 1 dog when given mercuhydrin, either alone or with ascorbic acid, died of ventricular asystole. The 1 animal in which ventricular fibrillation developed received the smallest amount of mercuhydrin.

Bundesen and his associates [3] reported the detoxifying effect of ascorbic acid on arsenical compounds in human beings and concluded that the addition of this substance, by its reducing effect, inhibited the

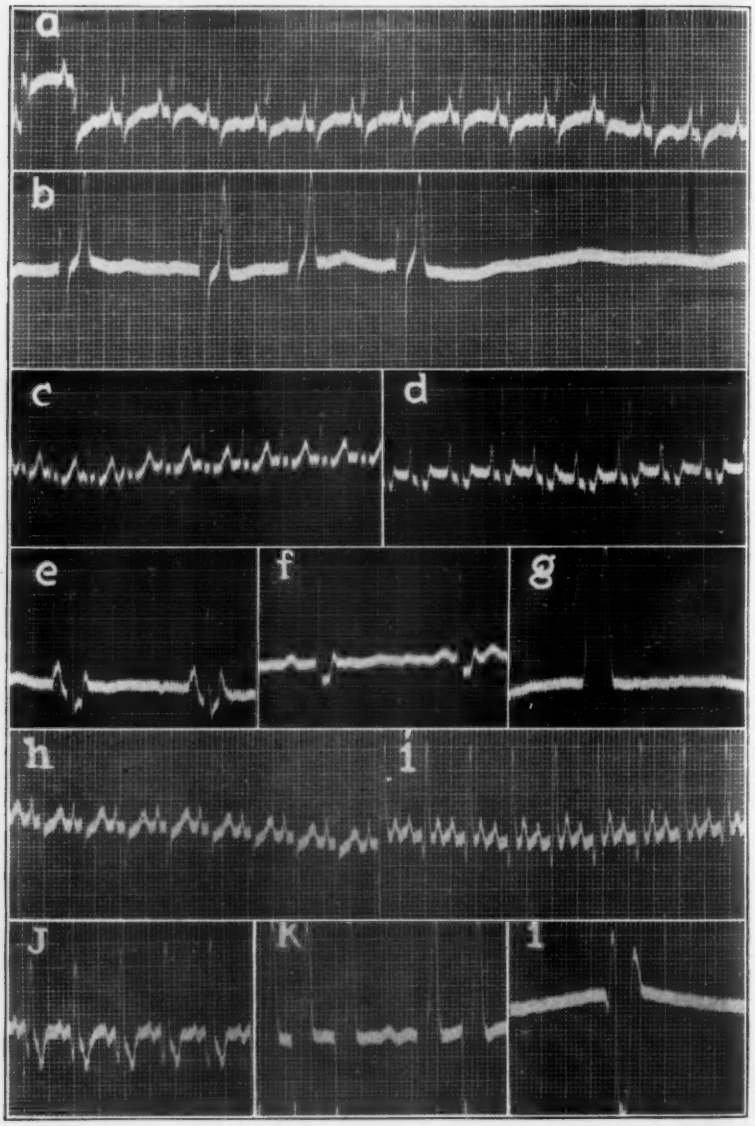

Figure 3

(See legend on opposite page)

oxidation of the arsenic radical. McChesney and others [8] investigated the effect of ascorbic acid on arsenicals in animals and also stated the belief that the detoxifying action was by this method. Marin [9] reported effective results in ascorbic acid therapy of nonfatal hypersensitivity reactions to mercury in human beings and found that ascorbic acid in vitro reduced the mercuric salt to mercurous salt and then to the inert metal.[10]

Ascorbic acid was given prior to and simultaneously with the administration of mercuhydrin, and the results were compared. A dose of 150 mg. of ascorbic acid given ten minutes before the injection of 1 cc. of this mercurial preparation had less detoxifying effect than when given simultaneously. McChesney and his associates [8] noted in animals that ascorbic acid gave the greatest protection when these substances were administered together. We, therefore, combined ascorbic acid with the mercurial preparations and administered them simultaneously in the remainder of the experiments.

8. McChesney, E. W.; Barlow, O. W., and Klinck, G. H., Jr.: The Detoxication of Neoarsphenamine by Means of Various Organic Acids, J. Pharmacol. & Exper. Therap. **80**:81 (Jan.) 1944.

9. Marin, J. V.: Ascorbic Acid Therapy of Mercurial Stomatitis Caused by Antisyphilitic Therapy with Report of Cases, Rev. méd. de Rosario **31**:1127 (Nov.) 1941.

10. Marin, J. V.: Ascorbic Acid Therapy of Acute Mercurial Intoxication in Guinea Pigs, Rev. Soc. argent. de biol. **17**:581 (Nov.) 1941.

EXPLANATION OF FIGURE 3

Fig. 3.—(*a*), lead II of a control at a rate of 150 per minute prior to intravenous administration of mercuhydrin at five minute intervals in a 7 Kg. dog. (*b*), relative bradycardia at a rate of 75 per minute, with idioventricular rhythm after injection of 10 cc. before ventricular asystole. (*c*), lead II of a control at a rate of 150 per minute prior to intravenous administration of mercuhydrin and ascorbic acid at two minute intervals in a 6.5 Kg. dog. (*d*), slightly altered ventricular complexes with incipient depression of the ST segment after injection of 18 cc. (8 cc. of mercuhydrin and 10 cc. of ascorbic acid), the calculated minimum lethal dose of mercuhydrin for the dog at this interval of injection. (*e*), relative bradycardia at a rate of 36 per minute with altered ventricular complexes and depression of the ST segment after injection of 27 cc. (12 cc. of mercuhydrin and 15 cc. of ascorbic acid), 50 per cent more than the minimum lethal dose. (*f*), similar recording after injection of 31.50 cc. (14 cc. of mercuhydrin and 17.50 cc. of ascorbic acid), 75 per cent more than the minimum lethal dose. (*g*), idioventricular rhythm and complexes before ventricular asystole after injection of 36 cc. (16 cc. of mercuhydrin and 20 cc. of ascorbic acid), 100 per cent more than the minimum lethal dose. (*h*), lead II of a control prior to intravenous administration of mercuhydrin and ascorbic acid at five minute intervals in a 6.5 Kg. dog. (*i*), similar record after injection of 22.50 cc. (10 cc. of mercuhydrin and 12.50 cc. of ascorbic acid), the calculated minimum lethal dose for the dog at this interval of injection. (*j*), altered ventricular complexes with depression of the ST segment after injection of 33.75 cc. (15 cc. of mercuhydrin and 18.75 cc. of ascorbic acid), 50 per cent more than the minimum lethal dose. (*k*), idioventricular rhythm and complexes after injection of 45 cc. (20 cc. of mercuhydrin and 25 cc. of ascorbic acid), 100 per cent more than the minimum lethal dose. (*l*), ventricular complexes immediately before ventricular asystole.

Doses of 250 mg. of ascorbic acid and 1 cc. of mercuhydrin given at two minute intervals increased the average minimal lethal dose of this mercurial preparation by more than 50 per cent. Ascorbic acid and mercuhydrin given at five minute intervals increased the average minimal lethal dose by 66 per cent. It is possible that, with longer intervals of time, use of ascorbic acid may have progressively increased this average. Pines and his associates [4] used intervals of thirty minutes in their investigation of the detoxifying effect of another substance, magnesium sulfate.

The results of our experiments suggest that the greatest cardiac toleration for a mercurial diuretic occurs with mercuhydrin, which is the least likely to induce ventricular fibrillation, and that the detoxifying value of ascorbic acid is greatest for this preparation.

A method of predicting a fatal reaction in human beings is not available. Nonfatal hypersensitivity reactions, tachycardia or premature ventricular systoles may occur after intravenous administration.[2] Because such manifestations may be premonitory signs of a fatal reaction, it is thought that mercuhydrin combined with ascorbic acid is the diuretic preferred in such cases.

Mercuhydrin had the least cardiac toxicity of the three mercurials employed, and the addition of ascorbic acid increased its lethal dose. We, therefore, investigated the diuretic effect of this combination in human beings. Modell [11] has previously found that mercuhydrin is as effective a diuretic as mercurophylline injection and that the optimum dose is 2 cc. Twenty patients with cardiac failure have been studied to date. Mercuhydrin in doses of 2 cc. has been mixed with 500 mg. of ascorbic acid (Abbott Laboratories) and administered intravenously, with a result equal to or an actual increase of the diuretic effect up to 50 per cent. This clinical investigation is being continued and will be reported later in detail.

SUMMARY

Mercuhydrin was the least toxic of the three mercurial diuretics studied. The administration of ascorbic acid prior to or simultaneously with mercuhydrin definitely reduced the toxicity of this preparation, but when given with mercurophylline injection and with mersalyl and theophylline it had no detoxifying effect.

The usual mechanism of death produced by mercuhydrin, with and without ascorbic acid, was ventricular asystole and by mercurophylline injection and mersalyl and theophylline was ventricular fibrillation.

Twenty patients in cardiac failure who have received mercuhydrin with ascorbic acid intravenously to date have had an equal or an increased diuresis up to 50 per cent.

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11. Modell, W.; Gold, H., and Clarke, D. A.: Quantitative Observations on Mercuhydrin and Mercupurin, J. Pharmacol. & Exper. Therap. **84**:284 (July) 1945.

EXPERIMENTALLY INDUCED INFECTIOUS HEPATITIS

Roentgenographic and Gastroscopic Observations

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THE OCCURRENCE of anorexia, nausea, vomiting and abdominal pain during the preicteric and early icteric phases of infectious hepatitis has suggested that involvement of the gastrointestinal tract may be an important feature of this disease. The fact that the etiologic agent of infectious hepatitis is eliminated in the stools of patients in the acute phase of the disease and may be transmitted experimentally by feeding such material to human volunteers adds supporting evidence to this concept.[1] More objective criteria have been afforded by the demonstration at autopsy of regional lymphadenopathy as well as edema and phlegmonous changes in the stomach and small and large bowel in fatal cases.[2]

In an effort to demonstrate changes in the gastrointestinal tract during infectious hepatitis, certain roentgenologic and gastroscopic

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Acknowledgment is made of the assistance and cooperation of the following agencies: Selective Service, Camp Operations Division; Civilian Public Service Unit No. 68; Civilian Public Service Unit No. 140, and the Connecticut State Hospital, Middletown, Conn.

These investigations were aided in part by the Neurotropic Virus Disease Commission of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, in the Preventive Medicine Service of the Office of The Surgeon General, United States Army, Washington, D. C.

1. (*a*) MacCallum, F. O., and Bradley, W. H.: Transmission of Infective Hepatitis to Human Volunteers, Correspondence, Lancet **2**:228 (Aug. 12) 1944. (*b*) Havens, W. P., Jr.; Ward, R.; Drill, V. A., and Paul, J. R.: Experimental Production of Hepatitis by Feeding Icterogenic Materials, Proc. Soc. Exper. Biol. & Med. **57**:206-208 (Nov.) 1944. (*c*) Neefe, J. R.; Stokes, J., Jr., and Rheinhold, J. G.: Oral Administration to Volunteers of Feces from Patients with Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis, Am. J. M. Sc. **210**:29-32 (July) 1945.

2. Pathology of Infective Hepatitis, editorial, Brit. M. J. **1**:17-18 (Jan. 6) 1945. Gowen, G. H.: The Epidemiology of Epidemic Hepatitis, Bull. U. S. Army M. Dept., January 1945, no. 84, pp. 41-50. Havens, W. P., Jr.: Unpublished data.

studies have been made. Pöschl [3] has reported alteration in the antral portion of the stomach and first part of the duodenum, interpreted as evidence of gastroduodenitis. The patients in whom these changes were found were far along in the course of their disease; 50 per cent of them had only scleral icterus left, and the other half were no longer jaundiced. More recently, Knight and Cogswell [4] reported gastroscopic observations, with changes generally interpreted as superficial gastritis in 7 out of 9 patients during the preicteric and early icteric phases of naturally occurring infectious hepatitis. The antral portion of the stomach was primarily involved and in some instances the fundus. Five of these patients had small aphthous ulcers, from 2 to 5 mm. in diameter, in the antrum and on the angularis. In contrast are the essentially normal observations of Bank and Dixon.[5] It is to be noted, however, that most of their patients had gastroscopy performed at least three weeks after the onset of hepatitis.

During the past eight months, experiments in the transmission of infectious hepatitis to human volunteers conducted by the Neurotropic Virus Disease Commission have offered an opportunity to study the appearance of the gastrointestinal tract at various times during the course of disease by roentgenogram and the gastroscope. It is the object of this paper to describe these observations.

MATERIALS AND METHODS

Subjects.—Twenty-one healthy male human volunteers ranging in age from 19 to 27 years were employed as experimental subjects. They were divided into two groups. Group I was composed of 9 subjects who had roentgenographic examination made of the stomach and duodenum at some time during the acute phase of their infectious hepatitis. Group II was composed of 12 men who had roentgenographic examination of the upper part of the gastrointestinal tract before experimental inoculation and again during the acute and convalescent phases of disease. Six of these men also had gastroscopic examinations before experimental inoculation and during the acute and convalescent phases of infectious hepatitis.

Virus.—The strain of infectious hepatitis virus used in this laboratory was originally obtained from the stool of a United States Army soldier (B. E.) who contracted epidemic infectious hepatitis in Sicily in 1943.[1b] It has been through four passages in human volunteers to date. This agent is filtrable through a Chamberland no. 2 filter and withstands heating to 56 C. (132.8 F.) for at least

3. Pöschl, M.: Röntgenuntersuchungen des Magen-Darmkanals bei Icterus infectiosus, Röntgenpraxis **14**:401-405 (Nov.) 1942.

4. Knight, W. A., and Cogswell, R. C.: Preliminary Observations of the Gastric Mucosa in Patients with Infectious Hepatitis, J. A. M. A. **128**:805 (July 14) 1945.

5. Bank, J., and Dixon, C. H.: Gastroscopy in Acute and Chronic Hepatitis, J. A. M. A. **131**:107 (May 11) 1946.

thirty minutes.[6] It has produced the disease in 27 out of 40 human volunteers (including this experiment) inoculated parenterally or orally, with periods of incubation ranging from fifteen to thirty-four days.

Infectious materials employed in this experiment were specimens of serum or stools obtained during the acute phase of disease experimentally induced in human volunteers. Infectious serum was fed or inoculated parenterally, and stool was fed.

Observation of Experimental Subjects.—All subjects were followed for periods of one hundred and ten to one hundred and fifteen days after inoculation. They were instructed to report at once the occurrence of any symptoms, which were then investigated. The volunteers who contracted infectious hepatitis were hospitalized in the Isolation Pavilion of the New Haven Hospital, under our supervision.

Laboratory Observations.—The following tests of hepatic function were performed at weekly intervals on all volunteers who received the material to be tested throughout the two periods of the experiment (four months each; the volunteers who reported symptoms or sickened had more frequent determinations made): (1) quantitative determination of total serum bilirubin content,[7] (2) cephalin-cholesterol flocculation test (Hanger),[8] (3) sulfobromophthalein dye retention test,[9] (4) thymol turbidity test,[10] (5) determination of urobilinogen[11] and determination of bilirubin content[12] in urine. Normal values for each volunteer were established before inoculation. Only volunteers who had symptoms and signs of infectious hepatitis in conjunction with consistently abnormal results in sulfobromophthalein dye retention tests and cephalin-cholesterol flocculation tests were regarded as showing positive evidence of infectious hepatitis. In this study all such patients had clinical jaundice.

RESULTS

When roentgenographic examinations were made on volunteers with experimentally induced infectious hepatitis, certain changes in

6. Havens, W. P., Jr.: Properties of the Etiologic Agent of Infectious Hepatitis, Proc. Soc. Exper. Biol. & Med. **58**:203-204 (March) 1945.

7. The quantitative total serum bilirubin determination was done according to the Method of Malloy and Evelyn (Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481-490 [July] 1937), the photoelectric colorimeter being used.

8. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation **18**:261-269 (May) 1939.

9. A 10 per cent retention in the blood thirty minutes after the intravenous injection of 5 mg. of bromosulfophthalein per kilogram of body weight was considered the maximum normal level (Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112-1114 [April 11] 1925).

10. Maclagan, N. F.: Thymol Turbidity Test: New Indicator of Liver Dysfunction; Preliminary Report, Nature, London **154**:670-671 (Nov. 25) 1944.

11. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698-725 (June) 1925.

12. Sparkman, R.: Studies of Urobilinogen: I. A Simple and Rapid Method for Quantitative Determination of Urobilinogen in Stool and in Urine, Arch. Int. Med. **63**:858-866 (May) 1939.

the duodenum were evident in some of them. These changes were: nonhomogeneous filling of the first portion and proximal part of the second portion of the duodenum, with an increase in the size of the mucosal folds and a corresponding narrowing of the troughs between the folds. There was fluoroscopic evidence of increased irritability of these segments. Filling by the opaque meal resulted in incomplete distention of the lumen and rapid emptying in some cases. In some patients who were severely sick, the prepyloric part of the stomach showed unbalanced peristalsis, coarse mucosal folds and accentuated transverse folds, as seen in cases of antral gastritis.

Group I.—Seven of the 9 volunteers in group I were examined roentgenographically during the preicteric or early icteric period of the

TABLE 1.—*Roentgenologic Findings in Nine Patients with Experimentally Induced Infectious Hepatitis*

Name	Roentgenogram: Stomach and Duodenum	Roentgenogram: Day of Jaundice	Abdominal Symptoms †
G. R.	Normal	1 20	+ 0
H. D.	Normal	2	+++
I. N.	Normal	1 22	++ 0
M. S.	Normal	2 19	+ 0
M. N.	Normal	21	0
H. S.	Normal	2 21	+ 0
F. W.	Duodenitis	—5*	+
S. R.	Duodenitis	8	+
J. S.	Gastroduodenitis	22	0

* Before jaundice.
† Degree of severity is indicated as follows: +, anorexia; ++, anorexia and nausea, and +++, anorexia, nausea and vomiting.

disease, and the remaining 2 were examined after three weeks of jaundice (table 1). The stomach and duodenum of all these patients were normal with the exception of 3 who showed changes compatible with antral gastritis or duodenitis. One man (J. S.) had incomplete filling of the prepyloric part of the stomach, with evidence of enlargement of the mucosal folds. The other 2 patients (F. W. and S. R.) had irregularity, with nonhomogeneous filling of the duodenal cap and increase in longitudinal folds. Coarsening and roughening of the folds of the second portion of the duodenum, with failure of this part to distend, were also evident. Since no preinoculation roentgenographic examinations were made on these 3 men, it is impossible to evaluate the significance of these findings. Moreover, such observations are similar to those made in a number of routine examinations done in cooperation

with Selective Service three years ago by the Department of Radiology, Yale University School of Medicine. At that time, changes were seen in a certain percentage of healthy asymptomatic selectees, similar to those shown in the stomach or duodenum of these 3 patients. Because of these atypical findings in the aforementioned selectees, it cannot be said that the changes in these 3 patients with experimentally induced infectious hepatitis are significant in the absence of control examinations before illness.

Group II.—Because of the difficulty in interpreting the findings when preinoculation roentgenographic examinations were not made, the

TABLE 2.—*Roentgenologic and Gastroscopic Findings in Patients with Experimentally Induced Infectious Hepatitis*

			Acute Phase						Convalescent Phase:
			Roentgenogram			Gastroscopy			
Volunteer	Period of Incubation, Days	Severity of Disease	Stomach and Duodenum	Day of Jaundice	Abdominal Symptoms	Stomach	Day of Jaundice	Abdominal Symptoms	Gastroscopy, Stomach
B. T.	23	+	Normal	4	+	Normal	3†	++	Normal
B. K.	26	+++	Normal	1†	++				
C. K.	26	++++	Gastroduodenitis	6	+	Normal	8	++	Normal
K. Y.	26	++++	Normal	11	0				
S. D.	24	++	Normal	5	0	Superficial gastritis	2†	+++	Normal
K. L.	30	+++	Normal	12	+				
B. S.	27	++	Normal	3	+++	Normal	6†	0	Normal
S. N.	21	++	Normal	2†	+				
V. W.	25	++++	Duodenitis*	7	+	Superficial gastritis	4	++	Superficial gastritis
I. G.	16	++	Duodenitis	1†	++				
T. R.	28	+	Gastroduodenitis	1	+	Superficial gastritis	7	0	Normal
W. E.	17	+	Duodenitis	2†	++				

* This patient (V. W.) also had roentgenologic evidence of duodenitis before experimental inoculation. Gastroscopic examination revealed normality at that time.
† Before jaundice.

12 subjects of group II had such examination made before experimental inoculation and during the acute phase of disease (table 2). A few of these patients were also examined again during convalescence. All were essentially normal before inoculation, except 1 man (V. W.) who had changes suggestive of duodenitis. When these 12 men were reexamined in the preicteric or early icteric period of their experimentally induced infectious hepatitis, the subject who had previously showed evidence of duodenitis had similar evidence at the second examination. Of the other 11 men, 7 were normal and in 4 there had developed changes in the duodenum compatible with a diagnosis of duodenitis.

Six men in this group also had gastroscopic examinations performed by one of us (S. D. K.) before experimental infection, during the acute phase of disease and again during convalescence. All 6 had normal-appearing gastric mucosa before experimental infection. During the acute preicteric or early icteric phase of disease, changes in the gastric mucosa compatible with a diagnosis of acute superficial gastritis developed in 3 of these men. The mucosa was fiery red and edematous, with small pools of grayish exudate between the folds. No ulcers were visible. In 2 of the men these changes had receded perceptibly in convalescence, while the third man still had residual change present seven weeks after onset of disease.

In this article are recorded the histories of the cases of 2 of the patients in whom evidence of gastritis and/or duodenitis developed during the acute phase of experimentally induced infectious hepatitis. Preinoculation studies of these patients had shown them to be normal.

REPORT OF CASES

Case 1.—S. D., a 26 year old healthy white man, contracted infectious hepatitis on Aug. 12, 1945, twenty-four days after ingesting 0.5 cc. of infectious serum. The onset was gradual, with intermittent cramplike abdominal pain and listlessness. Fever developed with a temperature of 103.6 F. (rectally) on the sixth day of disease, and clinical jaundice appeared on the twelfth day, persisting for eight days. The maximum measured height of total serum bilirubin was 1.4 mg. per hundred cubic centimeters. The course of the disease was mild, and recovery was complete. Preinoculation roentgenographic and gastroscopic examinations of the stomach and duodenum had revealed them to be normal. Gastroscopic examination on the tenth day of disease (August 21), when nausea and vomiting were present, revealed a normal antrum but a fiery red edematous mucosa in the body of the stomach. Small pools of grayish exudate were seen between the edematous folds of the mucosa. One week later, when the abdominal symptoms were ameliorated (August 27), roentgenographic examination of the stomach and duodenum showed normality. Eight weeks after onset, during convalescence, when the patient was asymptomatic, gastroscopic examination revealed a normal mucosa.

Case 2.—C. K., a 20 year old healthy white man, contracted infectious hepatitis (Aug. 14, 1945) twenty-six days after ingesting 0.5 cc. of infectious serum. The onset was acute, with anorexia, a temperature of 101 F. (rectally) and generalized fatigue. Clinical jaundice appeared on the sixth day of disease and persisted for twenty-seven days. The maximum measured height of serum bilirubin was 23.0 mg. per hundred cubic centimeters. The course of disease was severe, but recovery was complete. Preinoculation roentgenographic and gastroscopic examinations of the stomach and duodenum had revealed them to be normal. During the first week of jaundice, when the patient had anorexia and nausea, these examinations were repeated. The roentgenogram (August 24) revealed roughening and failure of homogeneous filling of the prepyloric part of the stomach. The duodenal bulb was ragged, without homogeneous filling, and there was an increase in the longitudinal folds. The proximal portion of the second part of the duo-

denum was tubular, without proper distention, while the distal second portion of the duodenum showed considerable increase in mucosal folds. Gastroscopy at this time (August 21) revealed normal gastric mucosa. During convalescence, when the patient was asymptomatic, seven weeks after onset of disease, gastroscopy was performed again, revealing a normal gastric mucosa.

COMMENT

In this paper, attention has been called to previous observations of others [13] on the occurrence of roentgenologic and gastroscopic changes in the stomach and duodenum of patients with epidemic infectious hepatitis. Similar examinations made in this laboratory on patients with experimentally induced infectious hepatitis have confirmed these findings. However, it has been pointed out that the appearance of changes supposedly characteristic roentgenologically of gastritis and/or duodenitis in patients with experimentally induced infectious hepatitis is of little significance unless previous control preinoculation studies have been made, since similar changes have been observed in a certain percentage of asymptomatic young men during examination for Selective Service. When preinoculation roentgenographic examinations were made in 12 healthy human volunteers, 1 was found to have changes suggestive of duodenitis. The fact that in 4 of the remaining 11 normal subjects there developed roentgenologic evidence suggestive of gastritis and/or duodenitis during the preicteric or early icteric period of their experimentally induced infectious hepatitis lends support to the concept that the gastrointestinal tract may be involved in the disease.

The development of gastroscopic evidence of acute superficial gastritis during the acute phase of hepatitis, with subsidence during convalescence, in 3 out of 6 of these subjects furnishes further confirmatory evidence. It is of interest that there was no particular correlation between gastroscopic and roentgenologic evidence of change. Of the 3 men who had gastroscopic evidence of acute superficial gastritis, the roentgenographic examinations showed normality in 1 and gastroduodenitis in the second; the third man (V. W.) had the same appearance roentgenographically before and after inoculation, although he had evidence of change from normal mucosa to acute gastritis by gastroscope. Of the 3 men who showed no demonstrable change gastroscopically in the acute phase of disease, roentgenologic evidence of duodenitis developed in 1, and the other 2 had normal roentgenograms of the gastrointestinal region. There was also no particular correlation between the severity of symptoms such as anorexia, nausea and vomiting and the presence of roentgenographic or gastroscopic changes. Nevertheless, our findings indicate that gastric changes do occur in this disease.

13. Pöschl.[3] Knight.[4]

SUMMARY

1. Roentgenographic examinations of the stomach and duodenum were made on 21 human volunteers with experimentally induced infectious hepatitis. Twelve of these men were also examined before experimental inoculation.

2. Of the 9 men without previous control examination, 3 had roentgenographic evidence of gastritis and/or duodenitis during the course of hepatitis.

3. Of the 12 men who had previous control examination, 1 showed evidence of gastroduodenitis before inoculation. In 4 of the remaining 11 there developed roentgenologic evidence of gastritis and/or duodenitis during the early phase of disease.

4. Six of these men had gastroscopic examination before inoculation and during the acute and convalescent phases of disease. Of these, gastroscopic evidence of acute superficial gastritis, which receded during convalescence, developed in 3.

5. No particular correlation was found between roentgenologic and gastroscopic changes in human volunteers with experimentally induced infectious hepatitis.

6. The gastroscopic findings indicate that acute inflammation of the wall of the stomach is one of the lesions of the acute stage of infectious hepatitis. Evidences of this lesion may last into convalescence.

EPILEPTOGENIC EFFECTS OF PENICILLIN

An Experimental Study

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IN 1945 Johnson and Walker [1] reported the death of a hydrocephalic child into whose cerebral ventricles large amounts of penicillin had been injected for treatment of an infectious condition. In this child status epilepticus had developed after administration of penicillin. This observation led Walker and his associates to carry out experimental studies [2] in which they demonstrated that penicillin may produce convulsions when brought into contact with cerebral tissue under a variety of conditions and in several species of animals.

A similar investigation has been made in our laboratory, and it is the purpose of this paper to present its results.

METHODS AND RESULTS

Dogs weighing 7 to 12 Kg. were used in all experiments. When operative procedures were involved, they were carried out with the animals under anesthesia induced by intravenous administration of pentobarbital sodium as separate procedures. Administration of penicillin was done on another day and without anesthesia or other medication in all instances.

The accompanying table shows the incidence of convulsions in all groups of experiments.

From the Department of Surgery, Vanderbilt University School of Medicine.

Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Vanderbilt University School of Medicine, and was partly aided by the Jack Fies Fund for Research in Neurosurgery.

The penicillin was furnished by Commercial Solvents Corporation, Lederle Laboratories, Inc., Merck & Company, Inc., and E. R. Squibb & Sons, at the direction of the Committee on Chemotherapeutic and Other Agents of the National Research Council.

1. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: Note of Warning, J. A. M. A. **127**:217-219 (Jan. 27) 1945.

2. Walker, A. E., and Johnson, H. C.: Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69-73 (Feb.) 1945. Walker, A. E.; Johnson, H. C., and Kollros, J. J.: Penicillin Convulsions: Convulsive Effects of Penicillin Applied to Cerebral Cortex of Monkey and Man, Surg., Gynec. & Obst. **81**:692-701 (Dec.) 1945.

The Epileptogenic Effects of Penicillin (0.1 cc. = 1,000 units)

Control Experiments, Isotonic Solution of Sodium Chloride			Subcortical Injection of Penicillin			Intracisternal Injection of Penicillin			Intraventricular Injection of Penicillin		
Dog. No	Dose (Cc.) and Site	Convulsions	Dog No.	Dose, Units	Convulsions	Dog No.	Dose, Units	Convulsions	Dog No.	Dose, Units	Convulsions
PC 16	0.2, cortex	0	PC 8	250	0	PC 6	5,000	+	PC 23	3,000	+++
PC 17	0.2, cortex	0	PC 9	250	0	PC 11	5,000	0	PC 13	5,000	++
PC 22	0.4, cortex	0	PC 9	350	0	PC 12	5,000	0	PC 24	5,000	++
PC 20	1.0, cistern	0	PC 9	400	0	PC 12	5,000	0	PC 7	5,000*	+
PC 21	1.0, cistern	0	PC 9	450	+++	PC 7	7,500	+	PC 18	5,000*	++++
			PC 9	500	+++	PC 11	7,500	++	PC 19	5,000*	+
Control Experiments, Autoclaved Penicillin			PC 8	500	+++	PC 12	7,500	++	PC 19	5,000*	++
PC 7	15,000, cistern	0	PC 19	500*	++	PC 12	7,500	++++			
PC 25	15,000, cistern	0	PC 26	500	+	PC 20	7,500	++			
			PC 8	1,000	+++	PC 26	7,500	+			
			PC 9	1,000*	++++†	PC 11	10,000	++			
			PC 14	1,000*	++++†	PC 25	10,000*	++++			
						PC 7	15,000	+++			
						PC 6	15,000*	++++†			
						PC 15	15,000*	++++			
						PC 10	25,000	++++†			
						PC 21	5,000	++			
						PC 20	7,500	++			
						PC 25	15,000*	++++			
						PC 27	5,000	0			
						PC 30	7,500	++++			
						PC 27	7,500	++++			

* Crystalline penicillin.
† Fatal convulsions.

Control Experiments.—In five experiments isotonic solution of sodium chloride was injected into the cerebral cortex or into the cisterna magna in similar volume and with the same technic as the injections of penicillin to be described hereafter. No convulsions or other abnormal neurologic manifestations were observed in any experiment.

In two other observations a solution of 15,000 units of penicillin which had been autoclaved at 15 pounds (6.8 Kg.) of pressure for forty-five minutes was injected into the cisterna magna of each animal, without significant results.

Furthermore, in many experiments previously reported [3] kaolin and other irritating substances which had been placed on the brain did not induce convulsive seizures. In other unpublished experiments by Hodge and Pilcher, subcortical injection of the animal's own blood was not followed by irritative phenomena.

Subcortical Injection of Penicillin.—In twelve experiments a small metal cannula was screwed into an opening in the skull in the parietal area on the left side to such a depth that it exactly reached the surface of the dura. Subsequently, sodium penicillin in a solution containing 1,000 units per 0.1 cc. was injected 2 to 3 mm. beneath the cerebral cortex.[4] Dosages from 250 units to 1,000 units were employed. As shown in the table, convulsions did not occur in any animal receiving less than 450 units of penicillin. In all animals receiving this amount or more convulsions were produced. The seizures began from two to ten minutes following injection and showed a consistent pattern. Profuse salivation occurred first and was followed by facial twitching, usually contralateral to the place of injection but sometimes bilateral. There rapidly followed hard generalized clonic convulsions, rising to a crescendo of violence and then subsiding somewhat, only to wax again into a violent fit. Duration of the convulsions was from forty-five minutes to three hours except in 2 animals receiving 1,000 units of penicillin each, both of which remained in status epilepticus until death ensued twelve and twenty-four hours respectively after injection.

Frequent passage of urine and feces and a variable increase in the temperature of the body were usually observed.

Penicillin could not be demonstrated in the cerebrospinal fluid in these animals, nor was there a significant rise in the cerebrospinal fluid cell count. As indicated in the table, crystalline penicillin was employed in some of the experiments of this and other groups, with results identical with those obtained with commercial preparations of the drug.

3. Meacham, W. F.; Angelucci, R.; Benz, E., and Pilcher, C.: Chemotherapy of Intracranial Infections: II. Clinical and Pathologic Effects of Intracranial Introduction of Sulfanilamide, Sulfathiazole and Sulfadiazine in Normal Dogs, Arch. Neurol. & Psychiat. **50**:633-651 (Dec.) 1943.

4. Knowledge of the length of the cannula and the length of the needle enabled the operator to gage the depth of injection accurately.

Injection of Penicillin Into the Cisterna Magna.—By the intracisternal route, the critical epileptogenic dose of a single injection of penicillin was 7,500 units (although in 1 animal mild convulsions developed after injection of 5,000 units). Convulsions were invariably produced by injection of 7,500 units or more and were extremely severe with larger doses (see the table). In 2 animals which received 15,000 units and 25,000 units respectively, the convulsions terminated fatally.

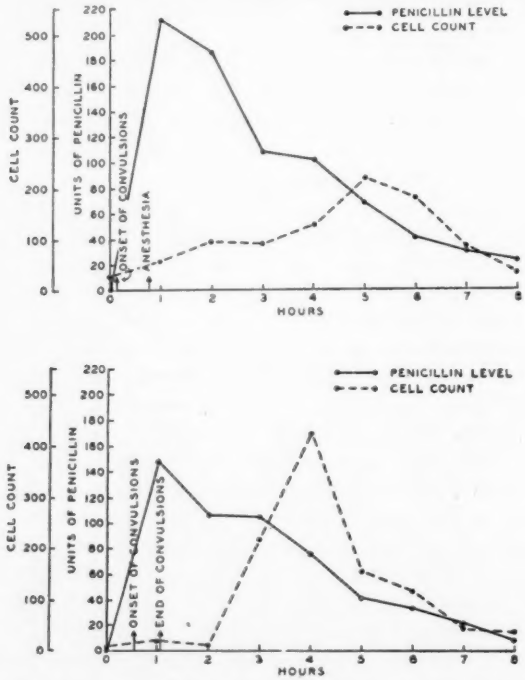

Chart 1.—The level of penicillin and the cell count in the cerebrospinal fluid following intracisternal injection of 7,500 units.

The seizures were slower in onset after intracisternal than after subcortical injection, usually beginning fifteen to thirty minutes after injection by the former route. The type of attacks and their duration were similar by the two routes.

That penicillin induces a pleiocytosis in the cerebrospinal fluid of dogs when injected intracisternally was reported by us in a previous communication,[5] and similar results were observed in human beings by

5. Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infections: III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin, J. A. M. A. **123**:330 (Oct. 9) 1943.

Rammelkamp and Keefer.[6] Such a pleiocytosis also occurred in all the experiments herein reported. The increase in cells usually began within an hour after injection of penicillin and reached its maximum eight or nine hours later (charts 1 and 2). The height of the cell count bore no relationship to the onset, duration or cessation of convulsions.

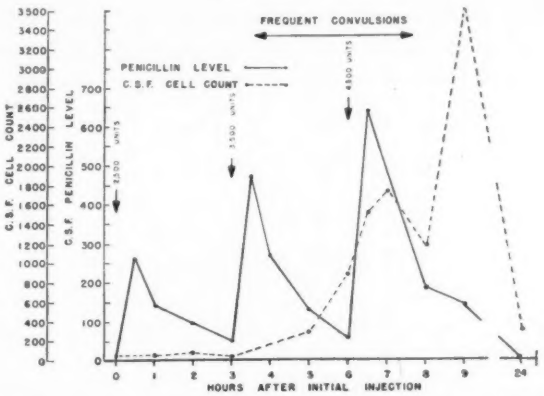

Chart 2.—The level of penicillin in the cerebrospinal fluid after intracisternal injection.

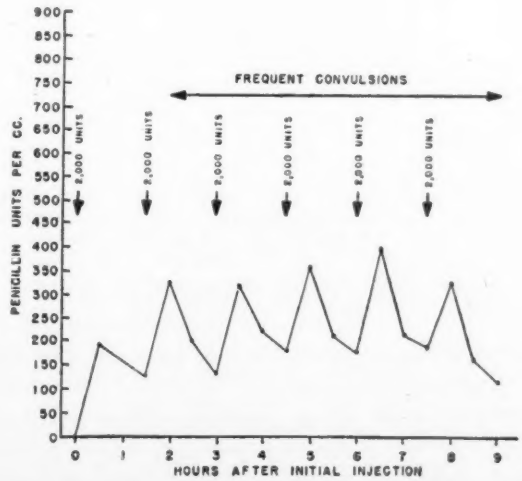

Chart 3.—The effects of frequent small intracisternal injections of penicillin.

6. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342-350 (March) 1943.

Furthermore, the cellular response varied with the reaction of the individual animal independently of the dosage of penicillin.

However, there did seem to be a relatively constant "convulsive level" of the drug in the cerebrospinal fluid, as indicated by the cisternal injection of doses of increasing magnitude (chart 2) or of frequent small doses (chart 3). In these and other experiments, it seemed that a level of 300 or more units of penicillin per cubic centimeter in the cerebrospinal fluid would invariably be accompanied by convulsive seizures in the dog.[7] Once the critical level was reached, however,

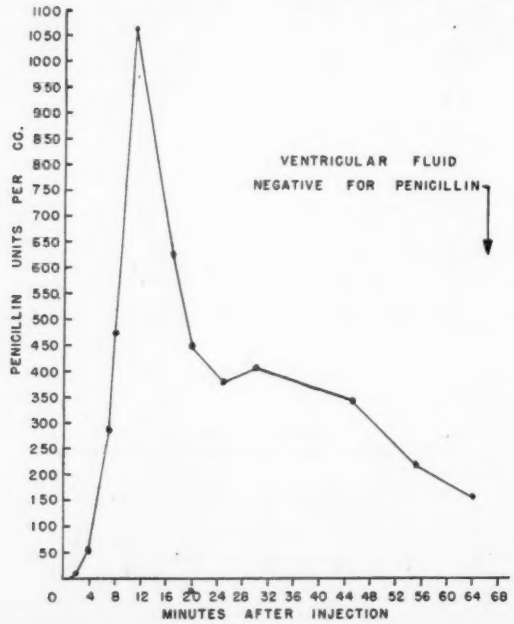

Chart 4.—The penicillin content of the cerebrospinal fluid over the cortex following injection of 10,000 units intracisternally.

convulsions might continue for some time after the level of the drug diminished (chart 3).

In several experiments it was possible to obtain specimens of cerebrospinal fluid from the subarachnoid space over the cerebral hemispheres after cisternal injection of penicillin. Assay of these specimens indicated extremely rapid diffusion of the drug over the cerebral cortex, a high level being reached in ten to twelve minutes (chart 4). These experi-

7. The graphs in chart 1 do not show the maximum level of penicillin, since the first specimens indicated were obtained one hour after injection.

ments also showed that penicillin injected into the cistern did not enter the ventricular system in detectable amounts.

Injection of Penicillin into the Lateral Ventricle.—Because of the difficulty of ventricular puncture in the normal dog, a series of animals was prepared by injection of lampblack into the cisterna magna, which induced a moderate degree of hydrocephalus within six to eight weeks. In these dogs it was possible to make injections into the ventricles with certainty and without significant trauma. Despite the irritating effects of the lampblack, its wide distribution in the subarachnoid space and the extensive fibrosis induced by it in the leptomeninges, none of the animals had convulsive seizures prior to the injection of penicillin.

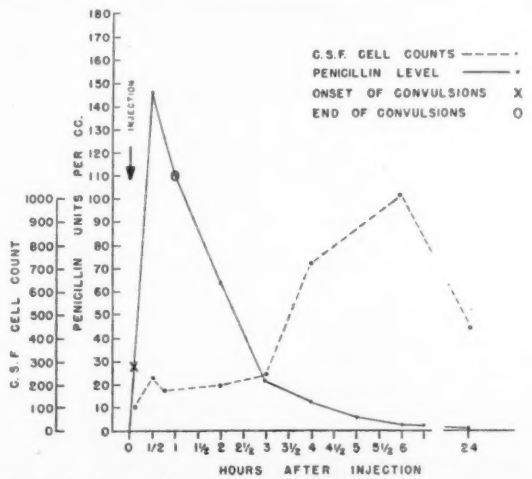

Chart 5.—The level of penicillin in the cisternal fluid, the cerebrospinal fluid cell count and the time of convulsions following intraventricular injection of 5,000 units.

In seven experiments on such hydrocephalic dogs, penicillin was injected into the lateral ventricle in doses of 3,000 to 5,000 units (see the table). In all instances convulsions developed within four to ten minutes. As would be expected, the drug appeared promptly in the cisternal fluid and the usual cellular reaction occurred (chart 5).

COMMENT

That penicillin can produce convulsions in the dog in the circumstances existing in our experiments is clear. Great caution is necessary, however, in interpreting these results in terms of possible harmful effects of the intrathecal or intracerebral use of penicillin clinically.

The critical epileptogenic dose of 7,500 units for a dog weighing 10 Kg. is equivalent to a dose of 52,500 units for a human being weighing

70 Kg. Although doses exceeding the latter amount have been reported to have been employed in a number of clinical cases, such dosage is far in excess of that usually advised. Further, it is true that dogs seem to be particularly susceptible to epileptogenic agents of various types. That the effects of penicillin are obtainable in other species is shown by the observations of Walker and Johnson.[2]

In our opinion, the experiments reported herein constitute a warning against excessive doses of penicillin by intrathecal administration, but they should not be construed as indicating that judicious intrathecal injection of penicillin is contraindicated.

SUMMARY

In dogs, large doses of penicillin injected into the cerebral cortex, into the cisterna magna or into the lateral ventricle produced violent and sometimes fatal convulsions.

The dosage required to produce convulsions varied according to the route of administration.

A critical level of 300 units of penicillin per cubic centimeter in the cerebrospinal fluid was necessary for the production of convulsions by intracisternal injection.

Book Reviews

Gastro-Enterology (in Three Volumes). By Henry L. Bockus, M.D., and Colleagues at the University of Pennsylvania Graduate School of Medicine. Volume III: **Diagnosis and Treatment of Disorders of the Liver, Gallbladder, Biliary Tract and Pancreas. Intestinal Parasites and Secondary Gastro-Intestinal Disorders.** General Index. Price, $35 per set of 3 volumes and separate desk index. Pp. 1,091, with 115 illustrations. Philadelphia: W. B. Saunders Company, 1946.

Volume 3 of this work is devoted to a consideration of diseases of the liver, biliary tract and pancreas and to parasitology and secondary gastrointestinal disturbances. As in the other volumes, there are preliminary chapters on the anatomy and physiology that are concerned with the various subjects. These are up to date and well documented. In the general discussion of disease syndromes, one finds much to commend and little to criticize. It is unfortunate that the section on infectious hepatitis was written just prior to the publication of so many studies in this field. The possibility that arsenical hepatitis may be due to transmission of the virus of hepatitis by contaminated syringes is, for instance, hardly mentioned. There is an excellent discussion of cirrhosis of the liver and of the metabolic diseases involving that organ.

The diseases of the gallbladder and the biliary passages are considered in great detail in some well written chapters. One may disagree with the authors in regard to the diagnostic value of duodenal intubation, but one can find no fault with their general presentation of the subject.

The section on pancreatic disease is particularly good and complete. One of the most valuable sections of the book has to do with gastrointestinal disturbances which are secondary to systemic disease and psychiatric conditions. This reviewer knows of no other work in which these subjects are so completely considered as in the volume under consideration.

The whole work is well illustrated, and there are many valuable tables and illustrations, such as the table on page 197, which presents in practical form the differential diagnosis between obstructive and hepatic cellular jaundice. There is an excellent chapter on the physiologic basis and interpretation of tests of hepatic function. The entire work is well documented with an excellent bibliography, and it has a general index. These three volumes should make an exceedingly valuable reference work for any one interested in the field of gastroenterology.

Skin Diseases, Nutrition and Metabolism. By Erich Urbach, M.D., and Edward B. LeWinn, M.D. Price, $12. Pp. 634, with 266 illustrations. New York: Grune & Stratton, Inc., 1946.

This book, the reviewer believes, represents a noteworthy attempt to relate disorders of the skin to more general disturbances of nutrition and metabolism. While much of the material will be found in other dermatologic treatises, the important thing here is that the author tries to get away from the old "botanical" classifications of dermatoses, made by inspection alone, and to penetrate literally as well as figuratively beneath the skin. To make this clear one may mention some of the chapter headings: "Influence of Diet on Metabolism of the Skin," "Allergy as a Cause of Skin Diseases" and "Dermatoses Due to Diseases of Liver and Pancreas." The book is well printed and illustrated, and there are numerous references. It should mark a step in advance in relating dermatology to internal medicine.

Electrocardiography in Practice. By Ashton Graybiel, M.D., and Paul D. White, M.D. Second edition. Price, $7. Pp. 458, with 323 illustrations. Philadelphia and London: W. B. Saunders Company, 1946.

Electrocardiography may be approached from two standpoints. First, there is the use and interpretation of the tracings by the general physician. He must know the elements of electrocardiographic interpretation and be able to recognize the changes of important conditions such as auricular fibrillation or complete heart block. Second, there is the study of the meaning in cardiac physiology of more esoteric changes in the electrocardiogram, and here one enters the field of research and the domain of the expert. While the present work is thoroughly done and deals comprehensively with the subject, its main purpose is still to help and instruct the physician in understanding and interpreting tracings. The general introductory matter, the abundant illustrations and the clinical notes all help in carrying out this purpose, and the book is to be highly recommended as an instructive and readable treatise, comprehensive enough but not going into controversial matters enough to confuse the practitioner.

A Manual of Tuberculosis: Clinical and Administrative. By E. Ashworth Underwood, M.D. Third edition. Price, $4.50. Pp. 540, with 88 illustrations. Baltimore: The Williams & Wilkins Company, 1945.

This well written manual of handy size but containing over five hundred pages describes in clear but simple form the subject of tuberculosis. The general principles of infection, clinical features and general treatment are followed by discussions of special forms of tuberculosis, epidemiology, laboratory methods and related subjects. The discussions seem to represent sound current opinion. The volume is handsomely printed, and there are numerous illustrations of pathologic material, roentgenograms, apparatus and equipment for sanatoriums.

Diseases of the Retina. By Herman Elwyn, M.D. Price, $10. Pp. 593, with 170 illustrations. Philadelphia: The Blakiston Company, 1946.

This new volume is divided into eight sections in which the author discusses vascular disturbances and malformations, hereditary degenerations, inflammatory disease, developmental anomalies, detachment, tumors and injury of the retina due to radiation. The clinical picture, ophthalmoscopic appearance, pathogenesis, pathologic changes, course and treatment are considered, and there are excellent illustrations of both the funduscopic and the microscopic appearance of all the commoner and many of the unusual conditions involving the retina. The section on degenerative changes on a hereditary basis is particularly comprehensive and places in one volume much material which has previously been available only from a number of sources.

By avoiding controversy, particularly as to the pathogenesis of the conditions, the author has condensed a huge amount of information in relatively few pages. The bibliography is representative, and the printer has done an excellent job.

Motor Disorders in Nervous Diseases. By Ernst Herz, M.D., and Tracy J. Putnam, M.D. Price, $3. Pp. 184. New York: King's Crown Press, 1946.

This small book is a "descriptive syllabus for study before and after viewing a projection" of teaching films prepared in the Department of Neurology at Columbia University and the Neurological Institute, New York. Even without the films, the clear, simple text and the two hundred and fifty well chosen illustrations constitute a brief atlas of the commoner motor neurologic disorders and a useful manual of clinical methods for their demonstration. Controversial matters are eschewed, and only elementary facts are presented. Somewhat trite for the well versed neurologist, the volume is nevertheless a worthy compendium of what the physician can and should know about the subject, as well as a valuable primer for the student.